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The Role of Atrial Fibrillation in Cognitive Aging:

A population-based study

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The role of atrial fibrillation in cognitive aging: A population-based study

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To Mike

To mom and dad

The opposite of every truth is just as true.

Hermann Hesse

ABSTRACT

The role of atrial fibrillation (AF) in brain and cognitive aging (e.g., cognitive decline and dementia) is still unclear. In this doctoral thesis, we aimed to investigate the temporal trends and potential determinants of dementia incidence, the occurrence of AF and the pattern of use of antithrombotic drugs, the association of AF with cognitive decline and dementia, and the association of AF with various structural brain abnormalities among older adults. Data were derived from the population-based Kungsholmen Project (KP), the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), and the SNAC-K MRI sub-study.

Study I. In the KP (1987-1989 to 1997-1998) and the SNAC-K (2001-2004 to 2010-2013) cohorts, 440 out of 1473 persons and 388 out of 1746 persons developed incident dementia, respectively. The incidence rate of dementia declined by 30% during the second decade (hazard ratio [HR] = 0.70; 95% confidence interval [CI]: 0.61-0.80). The decline was evident mainly among women and in people with low education. Vascular disorders and cognitive reserve factors explained only a small proportion of the decline (HR = 0.77, 95% CI: 0.65-0.90).

Study II. In SNAC-K, 328 (9.8%) of 3363 persons were ascertained to have AF at baseline. The prevalence of AF increased with advancing age and was slightly higher than previously reported. From 2001-2004 to 2007-2010, the use of anticoagulant drugs substantially increased among people with AF, especially in people with high risk of stroke or low risk of bleeding. However, still two-thirds of those at high stroke risk remained untreated with anticoagulants.

Study III. At baseline of SNAC-K, 243 (9.1%) of the 2685 dementia-free participants were identified to have AF. During the 9-year follow-up period, 279 (11.4%) people were ascertained to have incident AF and 399 (14.9%) developed incident dementia. As a time-varying variable, AF was associated with a faster annual decline in global cognition (β coefficient = -0.24, 95% CI: -0.31, -0.16) and a higher risk of all-cause dementia (HR = 1.40, 95% CI: 1.11-1.77) and vascular and mixed dementia (HR = 1.88, 95% CI: 1.09-3.23), but not Alzheimer's disease. Among participants with AF, use of anticoagulant drugs, but not antiplatelets, was associated with a reduced risk of dementia (HR = 0.40, 95% CI: 0.18-0.92).

Study IV. In the SNAC-K MRI sample, 39 (7.2%) of 540 people were identified to have AF at baseline. AF was associated with a higher odds ratio (OR) of the presence of cerebral infarcts (OR=3.98, 95% CI: 1.31-12.09). During the 6-year follow-up period, among 248 people who were free of cerebral infarcts, AF was associated with a faster increase in white matter hyperintensity volume (β coefficient = 0.45, 95% CI: 0.04-0.85) and lateral ventricular volume (β coefficient = 0.57, 95% CI: 0.13-1.02).

Conclusion. Dementia incidence had declined among older adults from the late 1980s to the early 2010s, and improved cardiovascular health and cognitive reserve could only partially explain the decline. In addition, AF is common in old age, and despite an increase in the use of anticoagulant drugs among older people with AF over time, still two-thirds of those with high risk of stroke remained untreated. Furthermore, AF is associated with an accelerated cognitive decline and a greater risk of dementia, and the use of anticoagulant drugs may prevent older patients with AF from developing dementia. Finally, AF is associated with a faster increase in white matter lesions and brain atrophy in the absence of cerebral infarcts.

Keywords: aging, atrial fibrillation, dementia, cognitive decline, prevalence, incidence, time trend, anticoagulant drugs, antiplatelet drugs, stroke risk, bleeding risk, cerebral small vessel disease, magnetic resonance imaging, population-based study

SAMMANFATTNING

Rollen av förmaksflimmer i hjärnan och kognitivt åldrande (t.ex. kognitiv nedgång och demens) är fortfarande oklar. I denna doktorsavhandling syftade vi till att undersöka tidstrender och potentiella faktorer för förekomst av demens, förekomsten av AF och mönstret för användning av antitrombotiska läkemedel, associeringen av AF med kognitiv nedgång och demens, samt associeringen mellan AF och olika strukturella hjärnabnormaliteter hos äldre vuxna. Data från det befolkningsbaserad Kungsholmen-projektet (KP), the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) och SNAC-K MRI- delstudie har använts i detta projekt.

Studie I. I KP (1987-1989 till 1997-1998) och SNAC-K (2001-2004 till 2010-2013) kohorterna, diagnosticerades 440 av 1473 personer respektive 388 av 1746 personer med demens. Förekomsten av demens sjönk med 30% under det andra decenniet (riskkvot [HR] = 0.70; 95% konfidensintervall [CI]: 0.61-0.80). Minskningen var tydlig främst bland kvinnor och personer med låg utbildning. Kärlstörningar och kognitiva reservfaktorer förklarade endast en liten del av nedgången (HR = 0.77, 95% CI: 0.65-0.90).

Studie II. I SNAC-K identifierades 328 (9.8%) av 3363 personer med AF vid baslinjen. Förekomsten av AF ökade med stigande ålder och var något högre än det som tidigare rapporterats. Från 2001-2004 till 2007-2010 ökade användningen av antikoagulantia avsevärt bland personer med AF, särskilt hos personer med hög risk för stroke eller låg risk för blödning. Men två tredjedelar av de med hög stroke risk förblev fortfarande obehandlade med antikoagulantia.

Studie III. Vid baslinjen för SNAC-K identifierades 243 (9.1%) av de 2685 demensfria deltagarna med AF. Under den 9-åriga uppföljningsperioden utvecklade 279 (11.4%) personer med incident AF och 399 (14.9%) demens. Som en tidsvarierande variabel förknippades AF med en snabbare årlig minskning av global kognition (ß-koefficient = -0.24, 95% CI: -0.31, -0.16) och en högre risk för demens av alla orsaker (HR = 1.40, 95 % Cl: 1.11-1.77) och vaskulär och blandad demens (HR = 1.88, 95% Cl: 1.09-3.23), men inte Alzheimers sjukdom. Bland deltagarna med AF var användning av antikoagulantia, men inte antiplateletter, associerad med en minskad risk för demens (HR = 0.40, 95% CI: 0.18-0.92).

Studie IV. I SNAC-K MRI-subgruppen identifierades 39 (7.2%) av 540 personer med AF vid baslinjen. AF var associerat med högre odds (OR) av cerebrala infarkter (OR = 3.98, 95% CI: 1.31-12.09). Under den 6-åriga uppföljningsperioden förknippades AF bland 248 personer som var fria från hjärninfarkt med en snabbare ökning av hyperintensitetsvolym av vit hjärnsubstans (ß-koefficient = 0.45, 95% CI: 0.04-0.85) och lateral ventrikulär volym (P-koefficient = 0.57, 95% Cl: 0.13-1.02).

Slutsats. Förekomsten av demens har minskat bland äldre vuxna från slutet av 1980-talet till början av 2010-talet, och förbättrad kardiovaskulär hälsa och kognitiv reserv kunde bara delvis förklara nedgången. AF är vanligt i ålderdom, och trots en ökning i användningen av antikoagulantia bland äldre med AF genom tiden, förblev två tredjedelar med hög risk för stroke fortfarande obehandlade. Dessutom är AF associerat med en snabbare kognitiv nedgång och en större risk för demens, och användningen av antikoagulantia kan förhindra att äldre patienter med AF utvecklar demens. Slutligen är AF förknippat med en snabbare ökning av skador i vit hjärnsubstans och hjärnatrofi i frånvaro av cerebrala infarkter.

Nyckelord: åldrande, förmaksflimmer, demens, kognitiv nedgång, prevalens, incidens, tidsutveckling, antikoagulantia, antiplateletter, strokerisk, blödningsrisk, cerebral småkärlsjukdom, magnetisk resonansavbildning, befolkningsbaserad studie

摘要

心房纤颤在脑结构改变和认知功能障碍中的作用仍不明确。在该博士论文中，我们研究了老年痴呆发病率的趋势和及其潜在决定因素、心房纤颤的患病率和房颤病人中抗血栓药物的使用情况、心房纤颤与认知功能下降和老年痴呆风险的关联、以及心房纤颤与脑结构改变的关联。该论文涉及的所有数据来源于基于斯德哥尔摩社区老年人群的 Kungsholmen Project（KP）、SNAC-K Study、以及嵌入 SNAC-K 的核磁共振成像子研究 SNAC-K MRI study。

课题一：在 KP 1473 名研究对象中，1987-1989 到 1997-1998 间有 440 个新发痴呆病例；在 SNAC-K 1746 名研究对象中，2001-2004 到 2010-2013 间有 388 个新发痴呆病例。老年痴呆的发病风险在第二个十年显著下降了 30%（HR = 0.70; 95% CI: 0.61-0.80），并在女性和低教育水平人群中尤为显著。心脑血管健康的改善和认知功能储蓄的提升只解释了一小部分老年痴呆发病风险的降低趋势（HR = 0.77, 95% CI: 0.65-0.90）。

课题二：在 3363 个参加 SNAC-K 基线调查的老年人中，328（9.8%）人被诊断患有心房纤颤。心房纤颤的患病率随着年龄的增加而显著增长并且高于既往研究。从 2001-2004 到 2007-2010 间，心房纤颤病人中抗凝血药的使用率显著升高，特别是在高中风风险和低出血风险的人群中。然而仍然有三分之二的高中风风险者没有进行抗凝血药物治疗。

课题三：SNAC-K 基线调查中， 2685 名研究对象无老年痴呆，其中 243（9.1%）人患有心房纤颤。在 9 年随访过程中，新发 279（11.4%）例心房纤颤和 399（14.9%）例老年痴呆。心房纤颤与认知功能下降呈显著相关（β coefficient = -0.24, 95% CI: -0.31, -0.16）。心房纤颤也与老年痴呆风险（HR = 1.40, 95% CI: 1.11-1.77）以及血管性和混合痴呆风险（HR = 1.88, 95% CI: 1.09-3.23）呈显著相关，但与阿兹海默症关联无统计学显著性。在心房纤颤患者中，使用抗凝血药与老年痴呆风险降低有关（HR = 0.40, 95% CI: 0.18-0.92），而抗血小板药的使用与老年痴呆风险关联无统计学显著性。

课题四：在 540 个参加 SNAC-K MRI 基线调查的人群中，39（7.2%）人患有心房纤颤。心房纤颤患者中脑梗塞（脑影像学诊断）风险较高（OR = 3.98, 95% CI: 1.31-12.09）。在 248 个参加 6 年随访并无脑梗塞的研究对象中，心房纤颤与大脑白质病变增加（β coefficient = 0.45, 95% CI: 0.04-0.85）以及脑室容积增高（β coefficient = 0.57, 95% CI: 0.13-1.02）呈显著相关。

结论：老年痴呆发病率从 1980 年代末到 2010 年代初呈下降趋势，心脑血管健康的改善和认知功能储蓄的提升不能完全解释此下降趋势。心房纤颤在老年人中比较普遍；虽然房颤病人中抗凝血药的使用率上升了，仍然有三分之二的高中风风险病人始终未使用抗凝血药。此外，心房纤颤与认知功能下降和老年痴呆风险有关联，而抗凝血药的使用能在房颤病人中大幅度降低老年痴呆的风险。在无脑梗塞的情况下，心房纤颤与脑白质病变和脑萎缩仍存在相关性。

关键词：衰老；心房纤颤；老年痴呆；认知功能下降；患病率；发病率；时间趋势；抗凝血药；抗血小板药；中风风险；出血风险；全脑小血管病变；核磁共振成像；队列研究

LIST OF SCIENTIFIC PAPERS

I. **Ding M**, Qiu C, Rizzuto D, Grande G, Fratiglioni L. Tracing temporal trends in dementia incidence over 25 years in central Stockholm, Sweden. *Under review.*

II. **Ding M**, Fratiglioni L, Johnell K, Fastbom J, Ljungdahl M, Qiu C. Atrial fibrillation and use of antithrombotic medications in older people: a population-based study. Int J Cardiol 2017;249:173-178.

III. **Ding M**, Fratiglioni L, Johnell K, Santoni G, Fastbom J, Ljungman P, Marengoni A, Qiu C. Atrial fibrillation, antithrombotic treatment, and cognitive aging: a population-based study. Neurology 2018;91:e1732-e1740.

IV. **Ding M**, Wang R, Kalpouzos G, Laukka EJ, Johnell K, Fratiglioni L, Qiu C. Atrial fibrillation and cerebral small vessel disease among older adults: a longitudinal population-based study. *Manuscript.*

OTHER PUBLICATIONS RELATED TO THE TOPIC OF THIS DOCTORAL THESIS

I. **Ding M**, Qiu C. Atrial Fibrillation, cognitive decline, and dementia: an epidemiologic review. Curr Epidemiol Rep 2018;5(3):252-261.

II. Fratiglioni L, **Ding M**, Santoni G, Berglund J, Elmståhl S, Fagerström C, Lagergren M, Sjölund B, Sköldunger A, Welmer A, Wimo A. Demensförekomst i Sverige: geografiska och tidsmässiga trender 2001-2013. Resultat från den svenska nationella studien om åldrande, vård och omsorg-SNAC. SNAC 2017.

CONTENTS

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AF	Atrial fibrillation
APOE	Apolipoprotein E gene
ATC	Anatomical Therapeutic Chemical
AUDIT	Alcohol Use Disorders Identification Test
BMI	Body mass index
CI	Confidence interval
ECG	Electrocardiogram
ESC	European Society of Cardiology
HR	Hazard ratio
ICD	International Classification of Diseases
INR	International normalized ratio
KP	Kungsholmen Project
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
OR	Odds ratio
PVS	Perivascular space
SCI	Silent cerebral infarct
SD	Standard deviation
SNAC-K	Swedish National study on Aging and Care in Kungsholmen
SVD	Small vessel disease
TIA	Transient ischemic attack
WHO	World Health Organization
WMH	White matter hyperintensity

1 INTRODUCTION

1.1 Population aging and the dementia epidemic

Due to dropping fertility rates and longer life expectancy, the world's populations are aging rapidly, with varying degree and pace of aging across countries.[1,2] According to the United Nations, just 9% of the global population was aged 60 years and above in 1990. This proportion has risen to 11% by 2010 and is projected to reach 23% by 2100. Globally, the number of people aged 60 years and older will double in size, reaching 1 billion in 2020 and surpassing 2 billion by 2100.[3] Notably, the oldest-old population (e.g., people aged 80 years and older) represents the fastest growing segment of the society, with the proportion increasing at a projected rate of 0.4% per decade from 2020 to 2100. In Europe, the proportion of oldest-old will be 5% in 2020, higher than the world average level (2%).[3,4]

As one of the most devastating disorders in old age, dementia refers to a clinical syndrome characterized by progressive decline in multiple cognitive domains that is severe enough to affect social or professional functioning. Advancing age is the strongest risk factor for dementia, and as a result of population aging, more and more older adults are at an increased risk of dementia. According to the World Alzheimer Report, 46.8 million persons worldwide were affected by dementia in 2015, and this number is expected to reach 75 million by 2030 and 132 million by 2050. In 2018, dementia has become a trillion dollar disease, and its global economic cost will rise to 2 trillion US dollars by 2030.[5] Given the projected vast increase in the future burden of dementia, WHO in 2012 had recognized dementia as a global public health priority. Global coordinated efforts, such as the London G8 Dementia Summit in 2013 and the first WHO Ministerial Conference on dementia in 2015, have been initiated to make effective response to the challenges of an increasing dementia epidemic.[6]

1.2 Is the incidence of dementia changing over time?

Despite the projected increase in the absolute number of people with dementia, a growing body of literature has suggested a potential decline in the incidence of dementia in Europe and North America.[7–9] Investigating the temporal trends in dementia incidence is challenging, as changes in diagnostic measures and other methodological aspects over time can affect the estimates and comparisons of dementia incidence.[10] Robust evidence needs to come from population-based cohorts using constant study designs and diagnostic measures over time.[9,11] So far, nine population-based studies worldwide, in which consistent study methods were used, have reported the temporal trends in the incidence of dementia in the UK,[12,13] the Netherlands,[14] France,[15] the USA,[16–19] and Japan

[20] (**Table 1**). Despite differences in study methods, all studies have indicated a declining trend in the incidence of all-cause dementia among older adults from the 1980s to the 2010s, except for a US study which reported a stable annual incidence of Alzheimer's disease (AD) from 1998 to 2012[19] and the Japanese study that showed an increasing incidence of all-cause dementia from 1988 to 2012[16]. On the other hand, studies using health administrative data have reported mixed results, where some studies supported a decreasing incidence of dementia [21–24] and others did not [25–28]. In Sweden, a register-based study of people aged ≥65 years showed an increase in the incidence of hospital diagnosis of dementia from 1987 to 2010, followed by a decline from 2010 to 2016.[26] So far direct evidence is lacking from population-based studies in Sweden on the temporal trends of dementia incidence, although a previous report using two population-based cohorts inferred a potential decline from the 1980s to the 2000s in Stockholm based on prevalence and survival data.[29] Furthermore, few studies have investigated whether and to what extent changes in dementia protective and risk factors over time could explain the observed decline. It has been suggested that improved formal education, better lifestyle, and successful primary prevention of cardiovascular diseases might be the driving force behind the decreasing risk of dementia.[9] Notably, owning to the effective preventative and therapeutic interventions for vascular risk factors, the incidence of stroke and major cardiovascular diseases has declined in Western Europe and North America over the past decades,[22,30,31] which might partly contribute to a decreasing incidence of dementia.

1.3 Atrial fibrillation in old age

Characterized by irregular activation and ineffective contraction of the atrium, atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting predominantly the older population.[32] It was estimated that AF confers a lifetime risk of 25% among people aged 55 years and above.[33] As the global population ages, AF constitutes a major public health challenge with increased risk of heart failure, myocardial infarction, stroke, and mortality.[34,35] According to the Global Burden of Disease Study, approximately 46 million people globally were estimated to have AF in 2016, a 40% increase from 34 million in 2010.[36,37] In the European Union, 9 million adults aged 55 years and over had AF in 2010, and this number was expected to double by 2060 to 18 million.[38]

1.3.1 The prevalence of atrial fibrillation

Table 2 shows a summary of major studies reporting age-specific prevalence of AF, where the prevalence increases successively with advancing age.[33,39–48] However, previously reported figures vary substantially across studies and countries. For instance, the prevalence of AF ranges from 2% to 10% in people aged 70-74 years and 3% to 12% in people aged 75-79 years; in the oldest old (age ≥80 years), the variations are even larger, spanning from 5% to 22%.

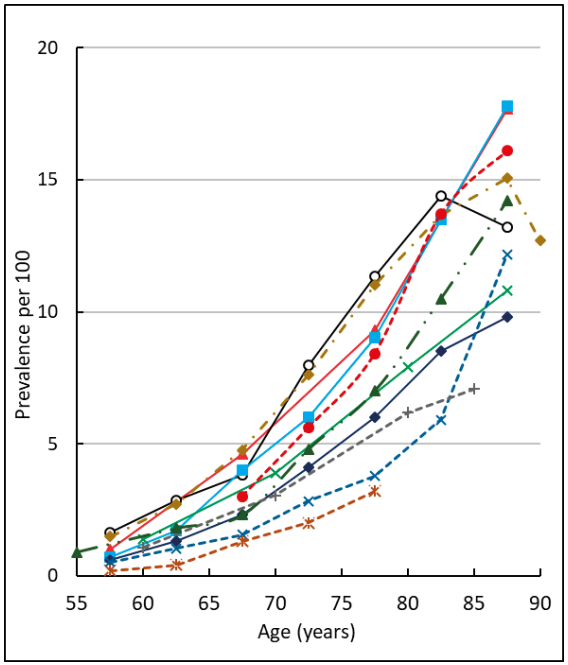
Comparisons of AF prevalence across studies might be hampered by differences in study populations and case ascertainment. Most available data concerning AF prevalence come from hospital samples, health registers, or people who were willing to take part in periodic health examinations. Studies based on these data are more likely to suffer from selection bias, therefore reporting relatively lower prevalence. In addition, AF is often undiagnosed due to silent AF and many people with AF may never come to medical attention,[49,50] therefore studies using only medical records to identify AF cases could have missed a big proportions of asymptomatic cases from the general population and thus underestimated the true prevalence. Only a few studies used population-based cohorts and multiple sources (e.g., medical records, electrocardiogram (ECG), and physical examination) to identify people with AF, and these studies generally reported higher overall and age-specific prevalence of AF.[33,39,51]

Table 1. A summary of population-based studies reporting temporal trends in dementia incidence

Study, year, country	Study population	Baseline cohorts	Diagnostic criteria	Temporal trends
Rajan et al. 2019,[19] USA	People aged ≥65 years living in outhern Chicago	Cycle 1: 1998-00 (n=842) Cycle 2: 2001-03 (n=643) Cycle 3: 2004-06 (n=734) Cycle 4: 2007-09 (n=656) Cycle 5: 2010-12 (n=415)	NINCDS-ADRDA for Alzheimer's disease	Stable
Sullivan et al. 2018, [18] USA	People aged ≥65 years living in rural Pennsylvania	1: 1987 (n=1681) 2: 2006 (n=1982)	Clinical Dementia Rating ≥1.0	Decline
Ahmadi-Abhari et al. 2017,[13] UK	People aged ≥50 years from the 1998-2001 Health Survey for England responders	Wave 1: 2002-03 (n=10525) Wave 2: 2004-05 (n=9225) Wave 3: 2006-07 (n=8155) Wave 4: 2008-09 (n=8386) Wave 5: 2010-11 (n=9767)	Either combination of cognitive impairment and ADL disability or self-report	Decline
Ohara et al. 2017,[20] Japan	People aged ≥60 years living in Hisayama	1: 1988 (n=803) 2: 2002 (n=1231)	DSM-III-R criteria	Increase
Matthew et al. 2016, [12] UK	People aged ≥65 years living in three areas of England	1: 1990-93 (n=7635) 2: 2008-11 (n=7762)	Algorithm (GMS-AGECAT)	Decline
Satizabal et al 2016,[17] USA	People aged ≥60 years living in Framingham	Period 1: 1977-83 (n=2457) Period 2: 1986-91 (n=2135) Period 3: 1992-98 (n=2333) Period 4: 2004-08 (n=2090)	DSM-IV criteria	Decline
Gao et al. 2016,[16] USA	African Americans aged ≥70 years in Indianapolis, USA; Yoruba aged ≥70 years in Ibadan, Nigeria	Indianapolis: 1: 1992 (n=1440) 2: 2001 (n=1835) Ibadan: 1: 1992 (n=1174) 2: 2001 (n=1895)	DSM-III and ICD-10 criteria	Decline in Indianapolis; no change in Ibadan
Grasset et al. 2016, [15] France	People aged ≥65 years living in Bordeaux	1: 1988-89 (n=1469) 2: 1999-2000 (n=2104)	Algorithm (based on MMSE and IADL) and DSM-III-R criteria	Algorithm: decline; DSM-III-R: no change
Schrijvers et al. 2012,[14] Netherlands	People aged ≥60 years living in Rotterdam	1: 1990 (n=5727) 2: 2000 (n=1769)	DSM-III-R criteria	Decline

MMSE=Mini-Mental State Examination; DSM=Diagnostic and Statistical Manual of Mental Disorders; IADL=Instrumental activities of daily living; ICD=International Statistical Classification of Diseases; GMS=Geriatric Mental State

Table 2. A summary of major studies reporting age-specific prevalence of atrial fibrillation



Authors	Country, study period	Study population
Heeringa et al. [33]	Denmark, 1990-93	Population-based study of people living in Rotterdam (n=6808)
Andersson et al. [39]	Sweden, 2011	All inhabitants of Northern Hälsingland (n=65532)
Majeed et al. [40]	UK, 1994-98	Patients registered in 211 general practices (n=1.4 million)
Carlo et al. [41]	Italy, 2016	All patients from three primary-care practices (n=4528)
Murphy et al. [42]	Scotland, 2001-02	Patients from 55 primary care practices (n=362155)
Wilke et al. [43]	Germany, 2007-08	Claims data of two mandatory insurance funds (n=8.3 million)
Go, et al. [44]	USA, 1996-97	People enrolled in a health maintenance organization (n=1.9 million)
Naccarelli et al. [45]	USA, 2004-05	Claims data from MarketScan and Medicare databases (n=21.6 million)
Zhou et al. [46]	China, 2000	Random sample of 14 cohorts from 13 provinces (n=29079)
Kodani et al. [47]	Japan, 2015	Participants in national health insurance and annual health checkups (n=12303)
Gomez-Doblas et al. [48]	Spain, 2010-12	Random sample of patients from 47 hospitals (n=8343)

1.3.2 Antithrombotic treatment in atrial fibrillation

The loss of effective atrial contraction can lead to formation of blood clots in the atrium, which tend to propagate to the brain.[52] It has been well established that AF substantially increases the risk of ischemic stroke.[35] However, this elevated risk of stroke is not homogenous and may change with the presence or absence of additional risk factors such as advancing age, prior stroke events, heart failure, and hypertension.[53,54] These factors have thus been used to build stroke risk stratification schemes, in which stroke risks are categorized into low, intermediate, and high risk strata in AF patients.[55] Generally, current international consensus guidelines suggest the initiation of anticoagulant treatment with either Vitamin K antagonists (e.g., warfarin) or novel oral anticoagulant drugs in people with intermediate or high risk of stroke. The use of antiplatelet therapy (e.g., aspirin) among older AF patients should be minimized, as the evidence for stroke prevention with antiplatelets in AF is weak, with a potential for harm, as compared to anticoagulant drugs.[56,57]

Risk stratification schemes. The most commonly used scheme for stroke risk assessment is the $CHADS_2$ score, which contains major clinical risk factors for stroke (scoring 1 point each for age ≥75 years, heart failure, hypertension, and diabetes and 2 points for ischemic stroke/transient ischemic attack (TIA)).[56] A $CHADS_2$ score ≥2 indicates high stroke risk, while a score of 1 and 0 indicates intermediate and low stroke risk, respectively.

The main drawback of the $CHADS_2$ score is that it does not reliably identify patients who are at "truly low risk" for stroke, as many patients with a $CHADS_2$ score of 0, hence do not need anticoagulation, still have an annual stroke rate of >1.5%.[54,58] The 2010 European Society of Cardiology (ESC) guidelines for AF management recommended the use of CHA_2DS_2-VASc score, in which more clinical relevant risk factors were added (scoring 1 point each for heart failure, diabetes, hypertension, vascular disorders including peripheral arterial diseases and myocardial infarction, age 65-74, and female sex, and 2 points each for age ≥75 years and ischemic stroke/TIA).[56] Multiple studies have shown that the CHA_2DS_2-VASc score is better at identifying "truly low risk" AF patients and performs the same as $CHADS_2$ score in terms of predicting stroke events.[54,59,60]

In addition to risk of stroke, decision-making for thromboprophylaxis also needs to balance the risk of major bleeding (e.g., intracranial hemorrhage), which is a complication of anticoagulant drugs and confers a high risk of mortality and disability.[61] Consensus guidelines have recommended the use of HAS-BLED score (1 point each for hypertension, abnormal renal function, abnormal liver function, ischemic stroke/TIA, major bleeding, labile international normalized ratio (INR), age ≥65 years, and 1 or 2 points for drug/alcohol use) to assess the risk of major bleeding for AF patients, and a HAS-BLED score ≥3 indicates a high bleeding risk.[56,57,62]

Underuse of anticoagulant drugs in patients with AF. Contrary to guideline-based expectations, AF patients are often under-treated in the real-world settings, and suboptimal use of anticoagulant drugs has been frequently reported. **Figure 1** shows the percentage of use of anticoagulant drugs in AF patients with a $CHADS_2$ score ≥2 or a CHA_2DS_2-VASc score ≥2 in previous investigations,[39,63–81] most of which are based on register data or hospital samples and very few used population-based cohorts. A proportion of anticoagulant therapy below 70% was reported in most of these studies using either scoring systems (**Figure 1**). For example, in two register-based studies in Sweden, around half of AF patients with high risk of stroke were using anticoagulant drugs 2006-2014.[71,77] The large-scale register-based studies of AF patients in the US showed that less than half of the patients were on anticoagulant treatment even among people with a $CHADS_2$ score >3,[76] and that untreated patients are at a greater risk of death and thrombo-embolism/TIA.[72] Physicians' concerns of major bleeding are one of the reasons behind the under-use of anticoagulant agents in older adults, yet very few studies have taken into account bleeding risk (e.g., HAS-BLED score) when assessing the patterns of anticoagulant therapy. However, a high HAS-BLED score *per se* should not be used to exclude AF patients from anticoagulant therapy but rather call for closer follow-up of the patients, as several studies have shown that the risk of thromboembolism without use of anticoagulant drugs substantially outweighs the risk of major bleeding with anticoagulant therapy.[82,83]

Apart from the worrisome underuse of anticoagulant drugs in AF patients, only a few studies have examined the secular change in the use of anticoagulant drugs.[75,84–87] Although a progressive improvement in the treatment of AF has been seen in several studies, many patients at high risk of stroke were still not receiving anticoagulant drugs. For instance, a US study using the Medicare data reported a significant annual increase from 1992 to 2002 in the use of warfarin coupled with a decline in the incidence of ischemic stroke among AF patients; yet still over 30% of AF patients were not on anticoagulant treatment by the end of follow-up.[85] A Japanese study reported that the prescription of warfarin among AF patients steadily increased from 41% in 2004 to 56% in 2010, but almost 40% of those with a $CHADS_2$ score ≥2 were not using anticoagulant drugs in 2010.[75] So far no population-based studies have examined this temporal trend considering both stroke and bleeding risk stratification schemes.

1.4 Atrial fibrillation and cognitive aging

Owing to the lack of curative treatment for dementia, exploring its modifiable risk factors has become a promising strategy to reduce the enormous economic and societal burden associated with cognitive dysfunction. Nine potentially modifiable risk factors over the life course (i.e., low education, hearing loss, hypertension,

diabetes, obesity, smoking, physical inactivity, social isolation, and depression) have been identified for AD and dementia. However, only 35% of all dementia cases are attributable to the combination of these modifiable risk factors, with another 7% accounted by apolipoprotein E (*APOE*) ε4 allele, the major genetic risk factor for AD.[88] Over the past two decades, continuous investigations have identified AF as a new yet important risk factor for cognitive decline and dementia among older adults.

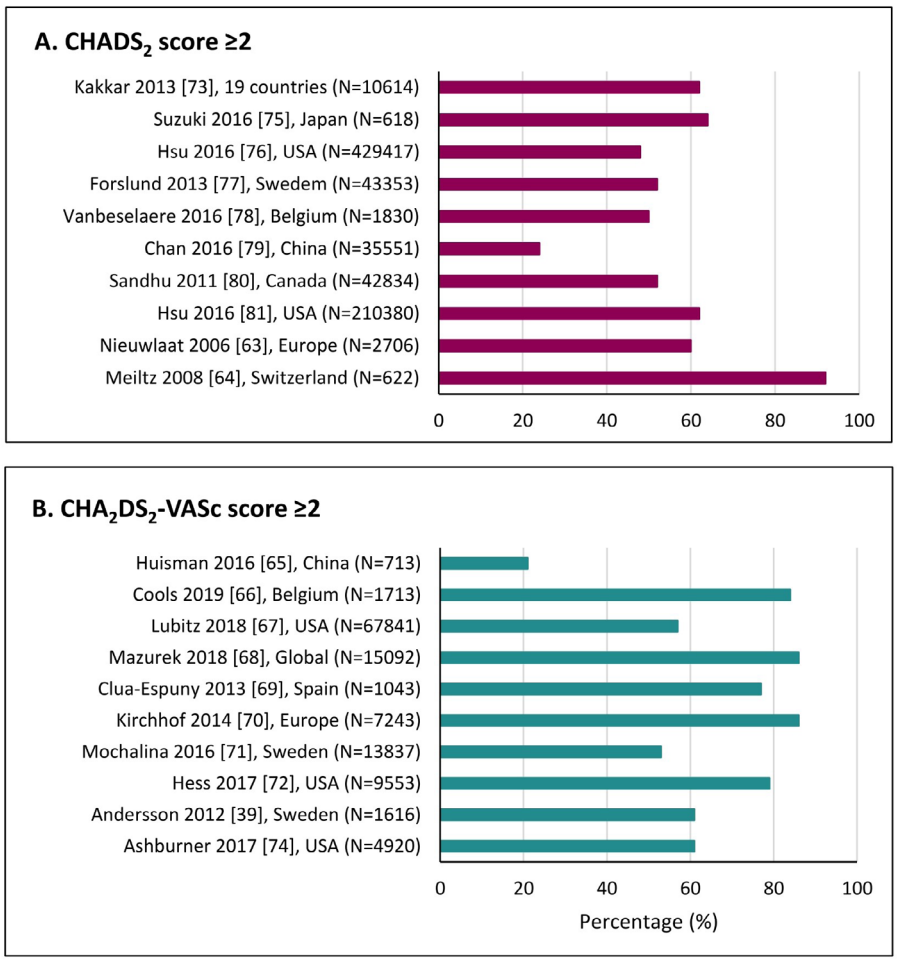


Figure 1. Percentage of use of anticoagulant drugs among AF patients with a $CHADS_2$ score ≥2 (A) or a CHA_2DS_2-VASc score ≥2 (B).

1.4.1 Atrial fibrillation, cognitive decline, and dementia

AF and dementia share a number of risk factors such as advancing age and cardiovascular risk factors including diabetes, hypertension, and high cholesterol.[89,90] AF increases the risk of ischemic stroke by 4- to 5-fold,[35] and the association between AF and dementia has been repeatedly reported among patients with a prior stroke.[91,92] During the past few years, evidence has emerged that AF may increase the risk of cognitive decline and dementia irrespective of the presence of stroke in the general older population.

Table 3 shows a summary of longitudinal studies examining the relationship between AF and cognitive decline or dementia;[93–106] these studies have substantial heterogeneity in study designs, case ascertainment of AF, and assessment of cognitive function. Nevertheless, most studies have reported an association of AF with an increased risk of cognitive decline and dementia, especially among younger-old people. For instance, the Rotterdam study including 6514 community-dwelling people followed up for 20 years found AF to be significantly associated with incident dementia only among people aged <67 years.[97] Similarly, the Whitehall II Study involving more than 7400 participants aged 45-69 years demonstrated that AF was associated with faster cognitive decline and higher risk of dementia over 26 years of follow-up.[96] More recently, the Atherosclerosis Risk in Communities (ARIC) study showed a faster annual cognitive decline associated with AF over 20 years among 12512 participants (mean age 57 years).[95] Among very old people (e.g., 75 years and above), results are rather mixed, where some studies report an association[100,106,107] and others do not.[102,104,105] Notably, incident AF has rarely been considered in previous studies; this is important given that the association between prevalent AF and dementia might be underestimated due to later diagnosis of AF and survival effect. In addition, although AF is presumed to affect the brain mainly through vascular pathways, a considerable proportion of dementia cases are attributable to both vascular and AD pathology in the brain [108,109] and very few studies have elucidated the association of AF with different dementia subtypes.

1.4.2 Do anticoagulant drugs prevent dementia in atrial fibrillation patients?

Oral anticoagulant drugs have been a potent and evidence-based treatment to prevent AF-related thromboembolism; by meta-analyses, warfarin is associated with a 64% decreased risk of stroke among AF patients compared to no treatment.[110,111] It is plausible that such treatment could also act against cognitive deterioration by reducing the number of cerebral infarcts. Whether AF-related dementia can be prevented by anticoagulant treatment has been under active investigations, yet there is still a paucity of evidence regarding the association of

anticoagulant drugs with cognitive outcomes. A meta-analysis in 2016 integrating data from one randomized controlled trial and four observational studies did not find sufficient evidence supporting an association of anticoagulant treatment with lower dementia incidence among AF patients.[112] In contrast, a recent Swedish register-based retrospective study including all AF patients in Sweden from 2006 to 2014 reported a 29% lower risk of incident dementia among patients using anticoagulant drugs compared to those not on anticoagulant treatment.[113] The inconsistent findings across studies could be due to substantial methodological variations; many studies suffer from high risk of bias including insufficient assessments of AF and cognitive endpoints, a short follow-up period, and high attrition rates.[112] Another challenge is that unlike cardiovascular outcomes such as stroke, the onset time of dementia is usually unclear due to its insidious onset and many people with dementia can remain undiagnosed for many years.[114] Therefore, evidence from longitudinal population-based studies is needed where AF, cognitive outcomes, and other health conditions are repeatedly assessed over time using comprehensive diagnostic tools.

Table 3. A summary of major longitudinal studies investigating the association of atrial fibrillation with cognitive decline and dementia.

Study, year, country	Study population	AF ascertainment	Assessment of cognitive outcomes	Main findings
Rydén et al. 2019 [93], Sweden	Gothenburg H70 Birth Cohort Studies; 12-year follow-up; age 70 years at baseline; N=561	ECG and ICD-8/9/10 codes	Dementia: DSM-III-R criteria	• AF was associated with higher risk of dementia both in the total sample (HR=2.8; 95% CI: 1.3-5.7) and in stroke-free subsample (HR=2.9; 95% CI: 1.2-6.8)
Kim et al. 2019 [94], South Korea	Korea National Health Insurance Service Senior cohort; 7-year follow-up; age ≥60 years at baseline; N=262611	ICD-10 codes	Dementia: Korean Dementia Screening Questionnaire and ICD-10 codes	• Incident AF was associated with greater risk of all-cause dementia (HR=1.52; 95% CI: 1.43-1.63), AD (HR=1.31, 95% CI: 1.20-1.43), and vascular dementia (HR=2.11, 95% CI: 1.85-2.41) • Use of anticoagulants was associated with lower risk of dementia (HR=0.61, 95% CI: 0.54-0.68) among people with incident AF.
Chen et al. 2018 [95], USA	ARIC study; 20-year follow-up; mean age 56.9 years at baseline; N=12515	ECG and ICD-9 codes	Cognitive function: a composite global Z score calculated from three neuropsychological tests Dementia: diagnostic algorithm, telephone interview, and ICD-9 codes	• AF was associated with faster decline in global cognitive Z score (between-group difference= 0.12, 95% CI: 0.03-0.23) • Incident AF was associated with greater dementia risk (HR=1.31, 95% CI=1.11-1.55)
Singh-Manoux et al. 2017 [96], UK	Whitehall II Study; 26.6-year follow-up; age range 45-69 years at baseline; N=10217	12-lead ECG and ICD-9/10 codes	Cognitive function: a global cognitive score combining memory, reasoning, and verbal fluency tests. Dementia: ICD-10 codes.	• People with longer AF duration experienced faster cognitive decline (p for trend=0.01) • AF was associated with incident dementia (HR=1.87, 95% CI: 1.37-2.55) among people free of stroke but not among those free of both stroke and coronary heart disease
de Bruijn et al. 2015 [97], The Netherlands	Rotterdam Study; 21-year follow-up; age ≥55 years at baseline; N=6514	ECG, physician diagnosis, and medical registers	Dementia: DSM-III-R criteria	• Incident AF was associated with higher risk of dementia only among people <67 years -(HR=1.81, 95% CI: 1.11-2.94) • Longer AF duration was associated with higher dementia risk only among people <67 years (p for trend=0.003)

Table 3. (continued)

Study, year, country	Study population	Assessment of AF	Assessment of cognitive outcomes	Main findings
Rusanen et al. 2014 [98], Finland	CAIDE study; mean 7.8-year follow-up; age range 65-79 years; N=1510	Medical registers	Dementia: DSM-IV criteria	• Prevalent AF was linked to highe risk of all-cause dementia (HR=2.61, 95% CI: 1.05-6.47) as well as AD (HR=2.54, 95% CI: 1.04-6.16); these associations were evident only among non-carriers of APOE ε4 allele.
Haring et al. 2013 [99], USA	RCTs of postmenopausal women; median 8.6-year follow-up; age ≥60years at baseline; N=7479	Self-reports or physical measure	MCI and probable dementia: DSM-IV criteria among those below education-adjusted cutoff of 3MSE score	• Prevalent AF was not associated with risk of probable dementia (HR=1.12, 95% CI: 0.59-2.14) or MCI (HR=1.46, 95% CI: 0.90-2.37)
Thacker et al. 2013 [100], USA	Community-dwelling people; mean 7-year follow-up; age 65+ at baseline; N=5150	ECG, ICD-9 codes	Cognitive function: modified MMSE (3MSE) and Digit Symbol Substitution Test	• Incident AF was associated with accelerated 5-year cognitive decline for age 70, 75, 80, and 85 years.
Marzona et al. 2012 [101], 40 countries	Two RCTs of patients with CVD or diabetes; median follow-up 56 months; mean age 66.5 years at baseline; N=31506	12-lead ECG	Cognitive function: MMSE; Dementia: new dementia diagnosis, reported severe cognitive impairment, or MMSE ≤23	• Prevalent and incident AF was associated with ≥3 points decline in MMSE score (HR=1.14, 95% CI: 1.03-1.26) • Prevalent and incident AF was associated with dementia (HR=1.30, 95% CI: 1.14-1.49)
Marengoni et al. 2011 [102], Sweden	Kungsholmen Project; 6-year follow-up; age ≥75 years at baseline; N=685	Physician diagnosis based on pulse rate, medical records (ICD-9), and medication use	Dementia: DSM-III-R criteria	• AF was associated with first-ever stroke but not incident dementia (HR=0.9, 95% CI:0.5-1.7) nor AD (HR=0.8, 95% CI: 0.4-1.5)
Bunch et al. 2010 [103], USA	Health care patients; mean 5-year follow-up; mean age 60.6 years at baseline; N=37025	ECG and ICD-9 codes	Dementia: ICD-9 codes	• Prevalent AF was associated with a greater risk of vascular dementia (HR=1.73, p=0.001), senile dementia (HR=1.39, p=0.005) and non-specific dementia (HR=1.44, p<0.001); the highest risk was seen in the younger age group (<70 years)

Table 3. (continued)

Study, year, country	Study population	Assessment of AF	Assessment of cognitive outcomes	Main findings
Peters et al. 2009 [104], UK	RCT of patients with hypertension; mean 2-year follow-up; age ≥80 years at baseline; N=3336	ECG	Cognitive decline: MMSE Dementia: DSM-IV criteria, a CT scan, and modified ischemic score	• Prevalent AF was not associated with incident dementia (HR=1.03, 95% CI: 0.62-1.72) or annual change in MMSE score (β coefficient=-0.26, 95% CI: -0.66, 0.13)
Rastas et al. 2007 [105], Finland	Community-dwelling people; 9-year follow-up; age ≥85 years at baseline; N=553	12-lead ECG at rest or 1-hour Holter ECG; health records	Dementia: DSM-III-R criteria	• Prevalent AF was not associated with incident dementia. • AF was not associated with amyloid load or neurofibrillary pathology
Tilvis et al. 2004 [106], Finland	Community-dwelling people; 10-year follow-up; age 75, 80, and 85 at baseline; N=650	Clinical examinations	Cognitive decline: increase in Clinical Dementia Rating class or decrease by at least 4 points in MMSE	• AF was associated with a 5-year cognitive decline (RR=2.88, 95% CI: 1.26-6.06)

AF=atrial fibrillation, ECG=electrocardiogram, CVD=cardiovascular disease, AD=Alzheimer's Disease, SNAC-K=Swedish Nation study on Aging and Care in Kungsholmen, FHS=Framingham Heart Study, ICD=International Statistical Classification of Diseases, DSM=Diagnostic and Statistical Manual of Mental Disorders, NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, MCI=mild cognitive impairment, CAIDE=Cardiovascular Risk Factors, Aging and Dementia, MMSE=Mini-Mental State Examination, RCT=randomized control trial, CT=computed tomography; HR=hazard ratio, RR=relative risk, OR=odds ratio, CI=confidence interval.

1.4.3 Cerebral small vessel disease as a potential mechanism

Several potential pathways linking AF to cognitive decline and dementia have been suggested. Cerebral hypoperfusion due to reduced cardiac output and cerebral thromboembolism resulting from pro-thrombotic and pro-inflammation state have been considered as the main AF-related cerebrovascular consequences, which can further lead to structure brain abnormalities manifested as cerebral small vessel disease (SVD).[90,115–117]

Cerebral SVD encompasses a group of pathological processes that affect brain small vessels including arterioles, small arteries, capillaries, and venules.[118,119] Features of cerebral SVD detected on neuroimaging devices such as magnetic resonance imaging (MRI) include cerebral infarcts, lacunes, enlarged perivascular spaces (PVS), white matter hyperintensities (WMH), and brain atrophy.[119] Importantly, cerebral SVD is a leading cause of all-cause dementia, and vascular and mixed dementia in particular,[120] and has been hypothesized as a potential mechanism linking AF to cognitive decline and dementia.[121] Despite the potential adverse effect AF imposes on the brain, very few longitudinal population-based studies have examined the association between AF and various cerebral SVD markers.

Cerebral infarcts. Extensive evidence has suggested a strong association between AF and cerebral infarcts.[122,123] While cerebral infarcts manifested as overt strokes are the most feared consequences of AF, silent cerebral infarcts (SCIs) are far more common than clinical stroke and were found in up to 90% of people with AF in small case series.[121] A meta-analysis of eleven studies found that AF was associated with an increased odds of SCIs, regardless of AF subtypes.[124] More recently, the ARIC study including 935 stroke-free middle-aged adults found that incident AF was associated with faster annual decline in word fluency only among people with prevalent SCIs; among people without prevalent SCIs, no association between incident AF and cognitive decline were found.[125] Another study including 1737 well-anticoagulated AF patients showed that the presence of SCIs have similar impact on cognitive function as clinical stroke.[123] These results suggested that the link between AF and cognitive deterioration might be partly explained by the presence or development of SCIs.

Lacunes and visible perivascular spaces (PVS). Lacunes are defined as round fluid-filled cavities that are between 3 and 15 mm in diameter, and PVS are defined as fluid-filled spaces between a vessel and the basal membrane of the glia limitans with a diameter often smaller than 3 mm; both lacunes and PVS have signals similar to that of cerebrospinal fluid.[119] While the underlying pathogenesis of lacunes and PVS have not been fully elucidated, current views suggest that both arise from vascular pathologies and are associated with several vascular risk factors. For instance, the ARIC study of 1827 individuals aged ≥55 years showed

that hypertension, diabetes, and ever smoking were significantly associated with the presence of lacunes.[126] A meta-analysis of 23 studies found that both hypertension and lacunes were risk factors for the presence of PVS.[127] Despite that lacunes and PVS might be of vascular origin, population-based studies have rarely investigated the association between AF and these two cerebral SVD markers.

White matter hyperintensities (WMH). Defined as hyperintense areas on T2-weighted or FLAIR images on MRI, WMH reflect a process of axonal loss and demyelination due to chronic cerebral ischemia. Clear evidence has shown that WMH predict increased risk of stroke and mortality, and that WMH are considered as one of the primary pathologies in vascular dementia.[128,129] Existing evidence for the association between AF and WMH mostly comes from cross-sectional studies, in which findings are not fully consistent. For example, pooled data from two population-based studies showed that AF was associated with periventricular WMH but not subcortical WMH,[130] while the ARIC study showed no significant association between AF and WMH after adjusting for vascular disease burden.[131] So far, evidence from population-based studies that supports a longitudinal association between AF and WMH is lacking.

Brain atrophy. Evidence regarding the association between AF and global and regional brain volumes are mixed. The Icelandic population-based AGES-Reykjavik Study showed that people with AF had lower total brain tissue, gray matter, and white matter volumes compare to those without AF; these associations were more profound among patients with persistent or permanent AF than those with paroxysmal AF, indicating a potential cumulative effect.[132] In the cross-sectional analyses of the Framingham Offspring study, AF was significantly associated with lower frontal brain volume even controlling for vascular burden and *APOE* ε4 status; however, this association was not statistically significant in the longitudinal analyses.[133] Notably, a cross-sectional study of 122 stroke-free AF patients (mean age 60 years) and 563 controls (mean age 64 years) showed that AF was associated with lower hippocampal volume but not total brain tissue and WMH volume after adjusting for vascular disorders and their treatment.[134,135]

1.5 Knowledge gaps

Findings from previous studies have collectively indicated important knowledge gaps regarding the temporal trend and its determinants in the incidence of dementia, as well as the role of AF in cognitive phenotypes and brain aging among older adults.

First, while some reports have demonstrated a declining dementia incidence in high-income countries, there is still a lack of direct evidence from population-based cohorts in Sweden regarding the temporal trends in the incidence of dementia.

Moreover, it is still unclear whether and to what extent changes in a variety of risk (e.g., vascular disorders) and protective (e.g., cognitive reserve) factors for dementia over time can explain the declining incidence.

Second, available estimates of AF prevalence mostly come from health administrative data and vary substantially across studies, and population-based studies are needed to estimate the age-specific prevalence of AF in the general older population. In addition, few population-based studies have examined the patterns and temporal trends of use of antithrombotic drugs among older people with AF using both stroke and bleeding risk scores.

Third, despite an established relationship between AF and a greater risk of dementia among stroke patients, longitudinal population-based studies are needed to clarify whether AF is associated with cognitive decline and dementia in the general older population regardless of clinical stroke. Furthermore, whether the use of anticoagulant drugs among older adults with AF reduces the risk of dementia remains unclear.

Finally, while clinical and silent cerebrovascular lesions have been proposed as an important mechanism linking AF to cognitive decline and dementia, few population-based studies have investigated the association of AF with a spectrum of cerebral SVD markers on MRI, such as lacunes, PVS, WMH, and brain atrophy.

2 AIMS

Hypothesis

This doctoral thesis is based on the following hypotheses: (i) the incidence of dementia has declined in the older population in central Stockholm from the 1980s to the 2010s, and risk and protective factors experienced over the life-course, such as early-life educational achievements, midlife health behaviors and cardiometabolic factors, as well as late-life cardiovascular disorders, may partly contribute to the decline; (ii) AF is associated with accelerated cognitive decline and a greater risk of dementia among older adults independent of clinical stroke and use of anticoagulant drugs is associated with a lower dementia risk among people with AF; and (iii) AF has an adverse impact on structural brain abnormalities manifested as cerebral SVD (e.g., WMHs, silent cerebral infarcts, and brain atrophy).

Overall aim

The overall aim of this thesis is to better understand the temporal trend and its determinants in the incidence of dementia and the associations of AF with accelerated cognitive and brain aging among older adults.

Specific aims

The following specific aims are addressed in the four individual studies included in the thesis:

i) To examine the temporal trend in dementia incidence in an older Swedish urban population from 1987 to 2013, and further, to identify factors that could partially explain such trend (*Study I*);

ii) To describe the prevalence of AF in the general older population and the patterns of use of antithrombotic medications in older adults with AF taking into account both stroke and bleeding risks (*Study II*);

iii) To investigate the longitudinal association of AF with cognitive decline and dementia among older adults, and to examine whether the use of anticoagulant drugs is associated with a lower risk of dementia among people with AF (*Study III*);

iv) To investigate the association of AF with various cerebral SVD markers in older people (*Study IV*).

3 MATERIALS AND METHODS

This doctoral thesis is based on data from the Kungsholmen Project (KP), the Swedish National study on Aging and Care in Kungsholmen (SNAC-K) population study, and the SNAC-K MRI study.

3.1 Population-based datasets

The Kungsholmen Project. KP is a longitudinal population-based study of aging and dementia.[136] On 1 October 1987, all 2368 residents, who were aged 75 years and older, living in institutions or at home in the Kungsholmen district of central Stockholm, were invited to attend the 2-phase designed survey at baseline (1987-1989), and 1810 (76.4%) people eventually participated. The baseline survey included a screening phase (phase I) where all participants undertook a Mini-Mental State Examination (MMSE) test, followed by a clinical phase (phase II) for people with an MMSE score ≤23 and a random sample of those with an MMSE score >23. Participants were then followed up every three years and data from 1987-1989 to 1997-1998 were used for the analysis of dementia incidence in Study I. **Figure 2** shows the study population of KP.

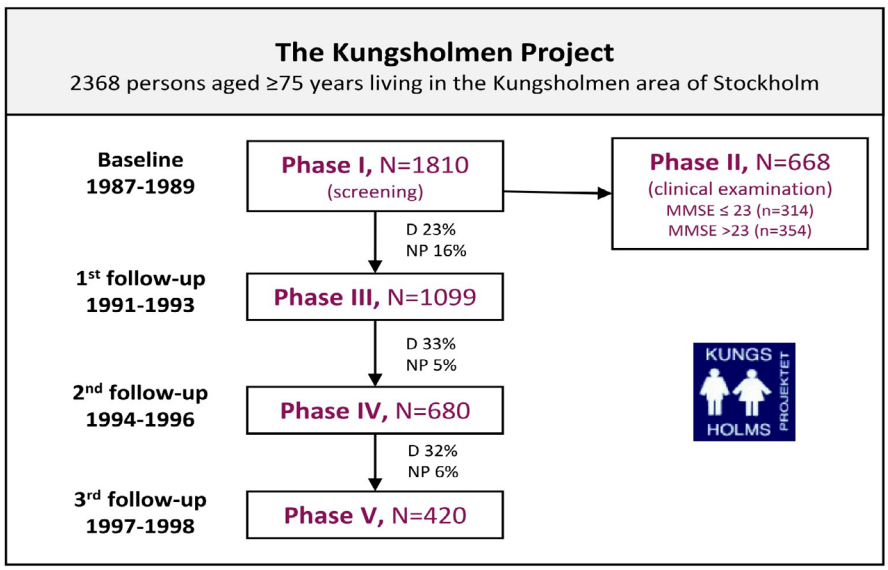


Figure 2. The study population and assessment waves of the Kungsholmen Project, 1987-1989 to 1997-1998. D=dead; NP=non-participants; MMSE=Mini-Mental State Examination

The SNAC-K population study. The SNAC-K study is a longitudinal population-based cohort of older adults aged 60 years and older who were living in institutions or at home in the Kungsholmen district of Stockholm.[137] At baseline, the target general population was divided into eleven age cohorts with a six-year interval in the younger cohorts (60, 66, and 72 years) and a three-year interval in the older cohorts (78, 81, 84, 87, 90, 93, 96, and ≥99 years), from which random samples were drawn from each of these age cohorts. A total of 4590 alive and eligible people were invited to participate and 3363 persons (response rate 73.3%) eventually took part in the baseline examination (2001-2004). Participants were then invited to follow-up examinations after six years for the younger cohorts (re-examined in 2007-2010) and every three years for the older cohorts (re-examined in 2004-2007, 2007-2010, and 2010-2013). **Figure 3** shows the study population of the SNAC-K project.

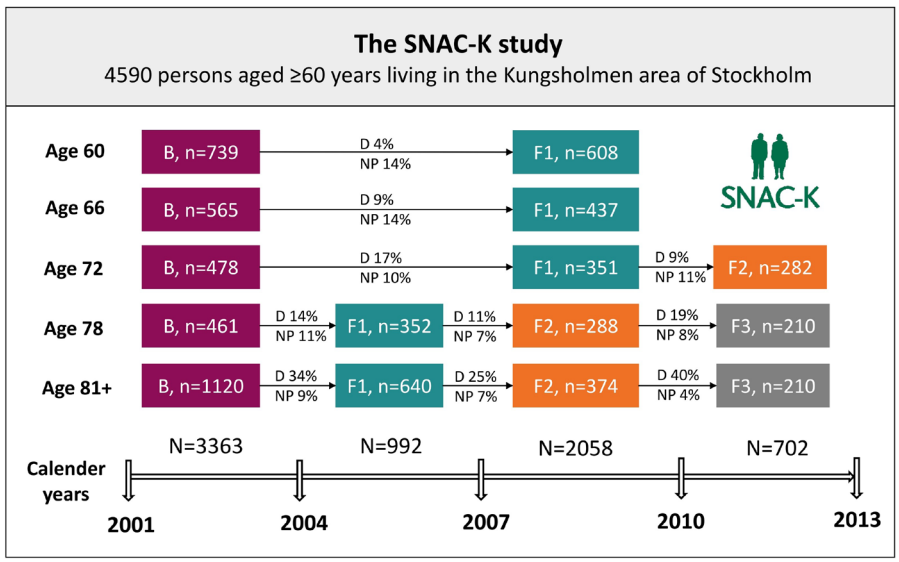


Figure 3. The study population and assessment waves of the SNAC-K study, 2001-2004 to 2010-2013. B=baseline; F1=1st follow-up; F2=2nd follow-up; F3=3rd follow-up; D=dead; NP=non-participants

The SNAC-K MRI study. During September 2001 to October 2003, SNAC-K participants who were non-institutionalized, non-disabled, and free of dementia were invited to undertake a structural brain MRI examination, and 555 individuals were scanned at baseline. Participants were invited to follow-up MRI examinations after six years (re-examined in 2007-2010) for the younger cohorts and every three years for the older cohorts (re-examined in 2004-2007 and 2007-2010).

3.2 Analytical samples

Figure 4 shows the flowchart of study samples included in each of the four individual studies. In Study I, 1473 dementia-free participants from the KP and 1746 from the SNAC-K who were aged ≥75 years were included in the analyses of dementia incidence. In Study II, all 3363 baseline participants from the SNAC-K study were included for the estimation of AF prevalence at baseline. In study III, a total of 2685 dementia-free SNAC-K participants were included for the association of AF with incident dementia. Study IV included 540 participants in the SNAC-K MRI study for the cross-sectional analyses at baseline and 248 participants for the longitudinal analyses over the follow-up.

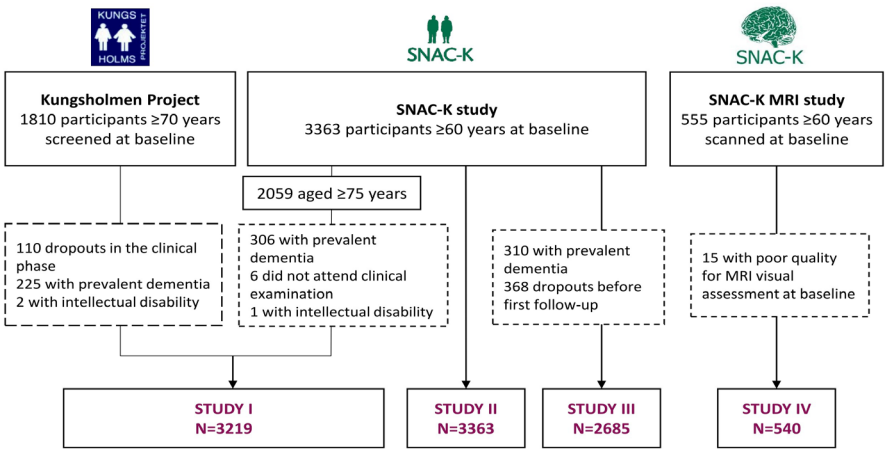


Figure 4. Flowchart of the study populations included in Study I-IV. The figure shows number of participants at baseline, people excluded from the analyses (in perforated boxes), and the final analytical samples.

3.3 Data collection and assessments

The KP and SNAC-K study followed similar protocols for data collection. Data were collected at baseline and follow-ups through clinical examinations, face-to-face interviews, and laboratory tests in accordance with standard procedures. Information on demographic characteristics (age, sex, and education), lifestyle factors (e.g., alcohol consumption, smoking habit, and physical exercise), chronic medical conditions (e.g., diabetes, hypertension, coronary heart disease, and heart failure), use of medications, and cognitive function were collected by nurses, physicians, and psychologists. For each study examination, physicians performed a comprehensive review of participants' health status based on results from the clinical examination, medical charts, self-reports, and information from proxies.

ICD-10 codes (International Classification of Diseases, Tenth Revision) were used to document diseases identified by the examining physicians. Data from the Swedish National Patient Register and Death Certificates were also linked to the SNAC-K and KP datasets to detect diseases before the baseline examination and during the follow-up period. During each study examination, participants were asked to bring their medication containers, and information on medication use at the time of visit were collected by the examining physicians and recorded according to the Anatomical Therapeutic Chemical (ATC) Classification System. Peripheral blood samples were taken, and genetic polymorphisms (e.g., *APOE* genotypes), total cholesterol, and glycated hemoglobin were examined at the university's laboratory.

3.3.1 Ascertainment of atrial fibrillation

AF was defined as a cardiac arrhythmia with the following characteristics on ECG: (i) irregular RR interval, (ii) no distinct P wave, and (iii) the interval between two atrial activations (when visible) is usually variable and <200 ms.[56]

In all studies included in this thesis, we identified AF cases through ECG and physician's diagnosis (ICD-10 code I48) at each study visit. Medical records from the patient registers (I48) were also used to detect the presence and the onset date of AF prior to the baseline examination as well as during the follow-up period. Since AF is a chronic disease, once AF is identified, participants were considered to have AF throughout the study period. In Study II, people with AF at baseline were considered to have prevalent AF, while people who developed new AF during the follow-up before the diagnosis of dementia, death, or end of follow-up were considered to have incident AF. We defined the onset date of AF as the time of first AF diagnosis identified either during study visits or through register records, whichever came first.

3.3.2 Stroke and bleeding scores

In SNAC-K, $CHADS_2$ score and CHA_2DS_2-VASc score were calculated to assess the risk of stroke among participants with AF. The $CHADS_2$ score ranges from 0 to 6 and consists of heart failure, hypertension, age ≥75 years, diabetes, and ischemic stroke/TIA (double points). The CHA_2DS_2-VASc score ranges from 0 to 9 and consists of heart failure, hypertension, age ≥75 years (double points), diabetes, ischemic stroke/TIA (double points), female sex, and vascular diseases (i.e., peripheral arterial diseases or myocardial infarction).[57] For both $CHADS_2$ and CHA_2DS_2-VASc, a score ≥2 indicates high stroke risk.

HAS-BLED score was used to assess the risk of bleeding.[138] Since data on labile INR is not available in the SNAC-K dataset, an incomplete HAS-BLED score was calculated: hypertension, abnormal renal function, abnormal liver function, ischemic stroke/TIA, major bleeding, age ≥65 years, excessive alcohol consumption, and use of medications including anti-platelet drugs (ATC code: B01AC) and nonsteroidal anti-inflammatory drugs (M01A and N02BA). The incomplete HAS-BLED score therefore ranges from 0 to 8, and a score ≥3 indicates high risk of major bleeding [6].

3.3.3 Assessment of study outcomes

Cognitive function and dementia

In both KP and SNAC-K, global cognitive function was measured using MMSE at each study examination.

For the diagnosis of dementia, a two-phase procedure was used to identify dementia cases at KP baseline [19]. In Phase 1 (the screening phase), all participants were screened using MMSE; in Phase 2 (the clinical phase), people who had an MMSE score <24 and a random sample of those who had an MMSE score ≥24 underwent comprehensive clinical examinations, cognitive tests, and laboratory tests. During the follow-up examinations of KP, all participants were directly examined instead. Dementia diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R) criteria following a validated 3-step procedure: the examining physician made a preliminary diagnosis of dementia based on the face-to-face interviews, clinical examinations, and cognitive tests; then a second physician independently made another preliminary diagnosis. In case of disagreement between the first two diagnoses, a third opinion was sought from a senior physician.[139]

In SNAC-K, all participants were examined using structured interviews, clinical examinations, and cognitive testing at each study examination. The same 3-step procedure as in KP was adopted in SNAC-K for the diagnosis of dementia following the DSM-IV criteria. Vascular dementia was diagnosed following the NINDS-AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherch´e et l'Enseignement en Neurosciences) criteria,[140] and AD was diagnosed in accordance with the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) criteria.[141] Because dementia cases are often caused by mixed pathologies of both cerebrovascular injuries and neurodegeneration,[142] participants who had a concurrent diagnosis of vascular dementia and AD were considered to have mixed dementia.

In both KP and SNAC-K, medical records for all participants and death certificates for participants who died during the follow-up were collected and reviewed by physicians to determine whether the participants died with dementia.

MRI markers for cerebral SVD

MRI protocol. In SNAC-K MRI study, eligible participants were scanned on a Philip Intera 1.5T MR scanner (Eindhoven, The Netherlands) at baseline and follow-ups. The protocol included a three-dimensional T1-weighted fast field echo (repetition time [TR] 15 ms, echo time [TE] 7 ms, flip angle [FA] 15°, field of view [FOV] 240, 128 slices with slice thickness 1.5 mm and in-plane resolution 0.94 × 0.94 mm, no gap, matrix 256×256), and an axial turbo fluid-attenuated inversion recovery sequence (FLAIR; TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, echo train length 21, FOV 230, 22 slices with slice thickness 5 mm and in-plane resolution 0.90 × 0.90 mm, gap 1 mm, matrix 256 × 256).[143]

Assessment of cerebral SVD markers. MRI markers of cerebral SVD included cerebral infarcts, lacunes, PVS, WMH, and brain volumes (e.g., global brain tissue volume and lateral ventricular volume). Cerebral infarcts, lacunes, and PVS were visually assessed by an experienced clinical neuroradiologist. Lacunes were identified on FLAIR images. PVS were identified in different brain regions (e.g., frontal lobe, hippocampus, basal ganglia, cerebellum, and parieto-occipital lobe) on T1, T2, and FLARE images. A second radiologist reviewed the MRI images of 18 subjects for PVS and this evaluation yielded a weighted κ of 0.77 (inter-rater reliability).[144] The number of PVS in all brain regions were then summed up and categorized into $\geq$10 and <10.[145]

T1-weighted images were automatically segmented into gray matter, white matter, and CSF using the improved unified segmentation algorithm in the SPM12 in MATLAB 10 (MathWorks Inc., MA, USA).[146] A specialist in neuroimaging analysis visually inspected all segmentations. Total brain tissue volume was calculated by adding gray matter and white matter volume. Lateral ventricular volumes were automatically segmented and estimated using the ALVIN toolbox, and were further visually verified for accuracy.[147] FreeSurfer image-analysis suite software version 5.1 was used to automatically segment the left and right hippocampi and calculate their volumes.[148] Global WMH volumes were manually drawn by a single rater on FLAIR images and were further interpolated on the corresponding T1 images to compensate for the gap between slices on FLAIR (mean Dice coefficient = 0.76).[149] All volumetric measurements were corrected using total intracranial volume.

3.3.4 Assessment of covariates

Demographic factors

Information on age, sex, and education of the participants was collected through baseline interviews. Education was assessed as highest attained level of formal education.

Lifestyle factors

Alcohol consumption was measured based on the frequency and amount of alcohol consumed on a typical drinking day, and was categorized as never or occasional, light/moderate, and heavy drinking. The Alcohol Use Disorders Identification Test (AUDIT) was also used to assess alcohol consumption, and an AUDIT score ≥8 indicates excessive alcohol consumption. *Smoking status* was assessed by asking the participants whether they had ever smoked, for how long they had smoked, and the number of cigarettes per day. Participants were categorized as never, former, or current smokers. *Physical exercise* was assessed through self-administered questionnaires by asking the participants whether they were regularly engaged in light, moderate, or intense exercises, and categorized as inactive (light and/or intensive exercise ≤2–3 times per month) and active (light, moderate, or intensive exercise several times per week). *Physical activity* was assessed through self-administered questionnaires by asking the participants whether they were engaged in any leisure activities with physical components (e.g., walking, gardening, and going to the museum) over the past 12 months, and was categorized into inactive (<1 time per month) and active (≥1 time per month).

Work complexity and psychosocial working condition

Information on job title, contents, employer, and time span of the longest-held jobs during adulthood was collected through a structured questionnaire.[150,151] Work complexity scores (i.e., with people, data, and things) for the longest-held job in adulthood were recorded according to a validated work complexity matrix, where higher scores indicate greater complexity [152]. Level of psychosocial working condition for the longest-held job during adulthood, including job control and job demand, was estimated using a validated job-exposure matrix [153]. Using the median score of job control and demands, participants were then categorized into four groups: high job strain (low control and high demands), low job strain (high control and low demands), passive job (low control and low demands), and active job (high control and high demands).

Cardiovascular risk factors

Weight and height of the participants were measured with light clothes and no shoes. *Body mass index* (BMI) was calculated as weight in kilograms divided by height in meters squared. In a sitting position, the participants were fitted with a sphygmomanometer and arterial blood pressure was measured twice on the left arm with a 5-miniute interval; the average of the two values was used in the analysis. *Diabetes* was defined as having glycated hemoglobin >6.4%, having a diagnosis from the examining physicians during study visits or from the patient register records (ICD-10 codes: E10–E14), or using diabetes drugs (ATC code: A10). *Hypertension* was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive drugs (ATC codes: C02, C03, C07, C08, and C09). *Dyslipidemia* was defined as having non-fasting total serum cholesterol ≥6.22 mmol/L or use of lipid-lowering drugs (ATC code: C10).

Chronic diseases

Heart failure, *abnormal liver function*, *cerebrovascular disease*, *ischemic stroke/transient ischemic attack (TIA)*, and *major bleeding* events (both gastrointestinal and intracranial) were identified through either physician's diagnosis during study visits or from the patient register records using ICD-10 codes. *Coronary heart disease* was defined as having a diagnosis from the examining physicians during study visits or register records or current use of nitrates (ATC code: C01DA) or ranolazine (C01EB18).[154] *Abnormal kidney function* was defined as having a physician's diagnosis at study visits or from register records, or having an estimated glomerular filtration rate <60 mL/min/1.73 m^2, which was calculated from the participants' serum creatine level.[155]

APOE genotype

APOE genotyping was performed using MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) analysis on a modified Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet. *APOE* genotype was grouped into carrying any ε4 allele vs. no ε4 allele.

3.3.5 Statistical analysis

Stata Statistical Software 14 or 15 (StataCorp LLC, TX, USA) was used for all analyses. In all studies, baseline characteristics were compared using χ^2 test for categorical variables and *t*-tests for continuous variables. The statistical significance level was set at two-tailed test $p<0.05$.

Study I. For both the KP and SNAC-K cohorts, 10-year follow-up data since the baseline examination were analyzed: 1987-1989 to 1997-1998 for the KP cohort, and 2001-2004 to 2010-2013 for the SNAC-K cohort. Cox regression models were performed to compare the incidence rate of dementia in the SNAC-K cohort to that in the KP cohort. To explore to what extent the changes in dementia incidence rate were attributable to changes in dementia protective and risk factors, Cox regression models were adjusted for age, sex, education, lifestyle factors, work-related factors, and chronic health conditions in the two cohorts.

Study II. At baseline, the age- and sex-specific prevalence of AF was estimated. Proportions of use of antithrombotic drugs (ATC codes: B01AA and B01AC) at baseline among participants with AF were calculated. To examine the temporal trend in the use of antithrombotic drugs, participants with AF who were aged over 66 years at baseline (2001–2004) and 6-year follow-up (2007–2010) were included. Logistic regressions were used to compare the proportion of use of antithrombotic drugs between baseline and 6 years later.

Study III. We used linear mixed-effects models to assess the association of AF with rate of annual decline in global cognition over the 9-year follow-up period; Cox proportional hazard regressions were used to examine the association of AF with incident dementia. In all models, AF was treated as a time-varying exposure where both prevalent and incident AF cases were considered. In order to minimize the influence of clinical stroke/TIA on the association between AF and dementia, we repeated the Cox regression models by excluding people with prevalent stroke/TIA diagnosis and censoring people at the dates when incident stroke/TIA occurred during the follow-up.

Among people with either prevalent or incident AF, propensity score-weighted Cox regressions were used to examine the association between use of antithrombotic drugs and incident dementia. The propensity score method was adopted to balance the characteristics that could differ between drug users and nonusers (i.e., baseline age, sex, education, heart diseases, kidney disorders, and MMSE score, etc.).[156] Lastly, we used the population attributable risk to estimate the proportion of dementia cases that could be hypothetically avoided if all AF patients had been in the treatment group.

Study IV. Logistic regression models were used to examine the across-sectional association of AF with the presence of cerebral infarcts, the presence of lacunes, and number of PVS (≥10 vs. <10) on MRI at baseline. Linear mixed-effects models were performed to estimate the annual changes in MRI volumetric measurements over the follow-up period in association with AF.

3.3.6 Ethical considerations

All phases of the KP and SNAC-K study as well as the linkage with patient registers and death certificates have been approved by the Ethics Committee at Karolinska Institutet and the Reginal Ethical Review Board in Stockholm, with the following registration numbers for KP: 87-148; 87-234 (Phases I & II), 90-251 (Phase III), 94-122 (Phase IV), 99-308 (Phase V), 99-025 (death certificate), and 01-020 (patient register), and SNAC-K: 01-114 (baseline), 04-929/3 (1st follow-up), Ö26-2007 (2nd follow-up), 2010/447-31/2 (3rd follow-up), and 2009/595-32 (register data).

Informed and written consent is collected from each and every participant of the KP and SNAC-K study; if the participant is severely cognitively impaired, the consent is given by a proxy (family members or guardians). During the examination process, the participants were assessed in a friendly and comfortable environment; if the participant expresses anguish or discomfort, the interview ends regardless of whether the participant or the proxy has given consent. The participants are also asked if they want to be informed of any disease detected during the examination, and in such cases, they are referred to their family doctors or other physicians. In addition, the participants are given feedback on the research conducted using the SNAC-K data, and this is done through various seminars held by researchers and booklets of scientific results.

All the data obtained from the participants become anonymous once they are digitalized from the questionnaires; this is done by giving each participant an artificial personal identification number, and all names and personnummer are removed. The original questionnaires are stored in locked safety cabins. All researchers working with the dataset respect and follow the ethical guidelines of the Swedish Council for Research in the Humanities and Social Sciences and the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki.

4 MAIN RESULTS

Below are brief summaries of the main results from each of the four individual studies included in this thesis. For more details on each study, please see the manuscripts and published articles at the end of the thesis.

4.1 Temporal trend in the incidence of dementia (Study I)

At baseline, a higher proportion of participants from the SNAC-K cohort than from the KP cohort never or occasionally consumed alcohol, had physical activities, were former smokers than current smokers, had active jobs, and had higher work complexity scores (age- and sex-adjusted $p<0.05$ for all). More people had diabetes and AF and less had hypertension in the SNAC-K cohort than in the KP cohort, while the proportions of participants with other cardiovascular or cerebrovascular conditions were not statistically different between the two cohorts.

Over the 10-year follow-up period, 440 (29.9%) out of 1473 participants in the KP cohort developed incident dementia from 1987-1989 to 1997-1998, and 387 (22.2%) out of 1746 persons in the SNAC-K cohort developed incident dementia from 2001-2004 to 2010-2013. The crude incidence rate of dementia was virtually lower in the SNAC-K than in the KP cohort across all age groups except for the oldest-old (≥90 years), among both men and women, and in both education levels (elementary school vs. middle school or above) (**Figure 5**).

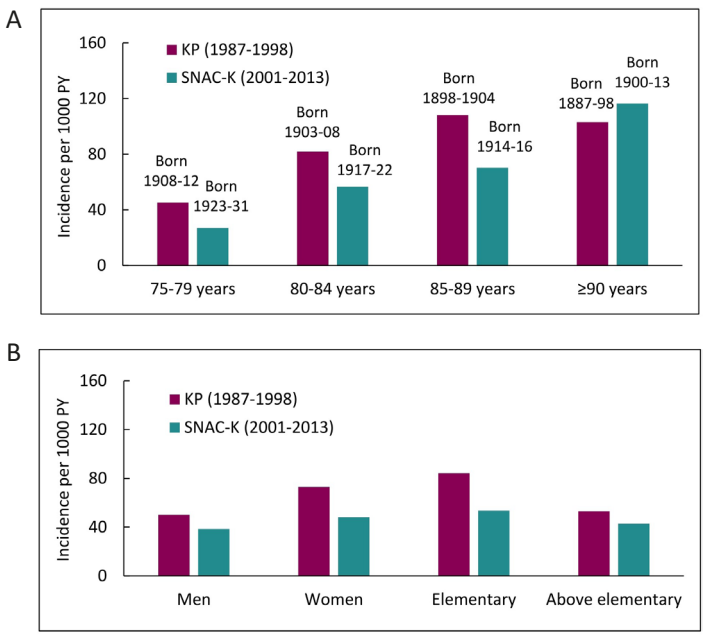


Figure 5. Incidence rate of dementia per 1000 person-years (PY) in the KP and SNAC-K cohort, stratified by (A) age groups and birth cohorts and (B) sex and education levels.

Cox regression models showed that the incidence rate of dementia was significantly lower in the SNAC-K than in the KP cohort after adjusting for age and sex (HR=0.70; 95% CI, 0.61-0.80), corresponding to an annual reduction of 3.0% in dementia risk. Further adjusting for education, lifestyle factors, work-related factors, and chronic diseases did not substantially change the results (HR=0.77, 95% CI: 0.65-0.90). In the stratified analyses, the incidence rate of dementia was significantly lower in the SNAC-K cohort than in the KP cohort in all age groups after adjusting for age and sex, except for age group ≥90 years where the incidence was unchanged. A significant decline in the incidence rate of dementia was also seen among women (HR=0.71, 95% CI: 0.59-0.86) and in people with elementary education (HR=0.57, 95% CI: 0.43-0.75) (**Table 4**).

Table 4. Hazard ratio (95% confidence interval) for incident dementia comparing the SNAC-K cohort (2001-2013) to the KP cohort (1987-1998) in the total population and stratified by age groups, sex, and education level

	Hazard Ratio (95% CI) of dementia for SNAC-K vs. KP cohort		
Characteristics	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Total population	0.70 (0.61-0.80)[d]	0.75 (0.65-0.87)[d]	0.77 (0.65-0.90)[d]
By age groups, years			
75-79	0.70 (0.55-0.89)[d]	0.82 (0.64-1.06)	0.92 (0.69-1.22)
80-84	0.66 (0.52-0.85)[d]	0.72 (0.55-0.94)[d]	0.69 (0.50-0.94)[d]
85-89	0.65 (0.44-0.96)[d]	0.65 (0.44-0.99)[d]	0.59 (0.38-0.93)[d]
≥90	1.17 (0.78-1.77)	1.16 (0.76-1.76)	1.00 (0.62-1.60)
By sex			
Men	0.82 (0.61-1.09)	0.88 (0.65-1.18)	0.94 (0.68-1.29)
Women	0.66 (0.56-0.77)[d]	0.71 (0.60-0.84)[d]	0.71 (0.59-0.86)[d]
By education level			
Elementary school	0.56 (0.43-0.72)[d]	0.56 (0.43-0.72)[d]	0.57 (0.43-0.75)[d]
Middle school or above	0.89 (0.74-1.07)	0.89 (0.74-1.07)	1.01 (0.72-1.43)

Missing values in covariates are imputed using multiple imputation. [a]Adjusted for age and sex.

[b]Adjusted for age, sex, and education. [c]Adjusted for age, sex, education, BMI, smoking, alcohol consumption, physical activity, work complexity, psychosocial working condition, hypertension, diabetes, ischemic heart disease, heart failure, atrial fibrillation, and cerebrovascular diseases. [d]$p<0.05$.

4.2 Prevalence of atrial fibrillation and use of antithrombotic Drugs (Study II)

A total of 328 (9.8%) out of 3363 participants at SNAC-K baseline (2001-2004) were classified to have AF. **Figure 6** shows the age- and sex-specific prevalence of AF, where the prevalence increased with advancing age, from 2.8% among people aged 60-66 years and 13.2% in those aged 81-87 years to 21.2% in people aged ≥90 years. The prevalence of AF was higher in men than in women in all age groups (age-adjusted OR=1.91, p<0.001).

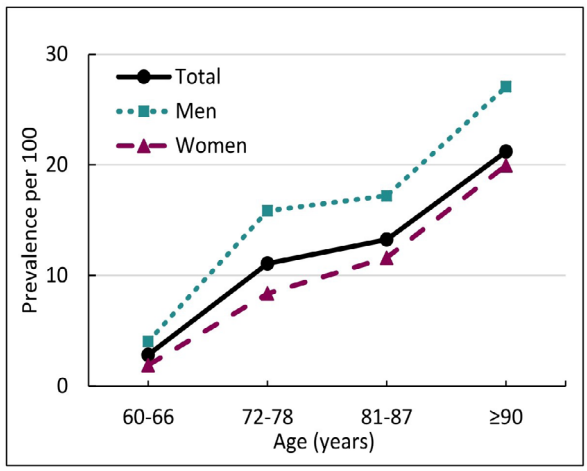


Figure 6. Prevalence of atrial fibrillation by age and sex at SNAC-K baseline (2001-2004)

Among participants with AF at baseline (n=328), 79.6% were classified as having high risk of stroke based on the $CHADS_2$ score and 97.3% according to the CHA_2DS_2-VASc score. Among AF patients with intermediate risk of stroke ($CHADS_2$=1), 17.0% were taking anticoagulant drugs and 39.6% were using antiplatelet drugs. Of people with $CHADS_2$ score ≥2, 25.4% and 53.5% were taking anticoagulant drugs and antiplatelet drugs, respectively. Re-grouping the participants using the CHA_2DS_2-VASc score did not substantially change the proportions of drug use in the high-risk group (**Table 5**). Of note, among AF patients with $CHADS_2$ score ≥2 at baseline, having a HAS-BLED score ≥3 was associated with not using anticoagulant drugs (multi-adjusted OR=2.66, 95% CI: 1.08–6.53).

Table 5. Use of anticoagulant and antiplatelet drugs among people with atrial fibrillation at baseline (2001-2004), stratified by levels of stroke and bleeding risk

Risk stratification	No. of AF cases	Anticoagulant drug use		Antiplatelet drug use	
		n	% (95% CI)	n	% (95% CI)
Total population	327	75	22.9 (18.4-27.5)	160	48.9 (43.5-54.3)
$CHADS_2$ score					
Low risk (0)	14	0	0.0 (0.0-0.0)	0	0.0 (0.0-0.0)
Intermediate risk (1)	53	9	17.0 (6.9-27.1)	21	39.6 (26.5-52.8)
High risk (2-6)	260	66	25.4 (20.1-30.7)	139	53.5 (47.4-59.5)
CHA_2DS_2-VASc score					
Low risk (0)	3	0	0.0 (0.0-0.0)	0	0.0 (0.0-0.0)
Intermediate risk (1)	6	0	0.0 (0.0-0.0)	1	16.7 (0.4-64.1)
High risk (2-9)	318	75	23.6 (19.0-28.6)	159	50.0 (44.4-55.6)
HAS-BLED score[a]					
Low risk (0-2)	89	28	31.5 (21.8-41.1)	8	9.0 (3.0-14.9)
High risk (3-8)	238	47	19.7 (14.7-24.8)	152	63.9 (57.8-70.0)

[a]The HAS-BLED score does not include labile INR.

Over the six-year follow-up period (2001-2004 to 2007-2010), the proportion of use of anticoagulating drugs significantly increased among AF patients with CHA_2DS_2-VASc score ≥2 (23.0% vs. 33.1%, p=0.008), and among those who had a HAS-BLED score <3 (32.0% vs. 52.5%, p=0.004). No significant change was observed in the use of antiplatelet drugs among participants with AF during this period (49.5% vs. 45.8%, p=0.423) (**Table 6**).

Table 6. Use of anticoagulant and antiplatelet drugs among people with atrial fibrillation in 2001-2004 and 2007-2010, respectively

Risk stratification	Year 2001-2004		Year 2007-2010		p[b]
	N/n[a]	% (95% CI)	N/n[a]	% (95% CI)	
Use of anticoagulant drugs					
Total (age ≥66 years)	313/71	22.7 (18.0-27.3)	308/101	32.8 (27.5-38.0)	0.005
$CHADS_2$ score					
Low risk (0)	10/0	0.0 (0.0-0.0)	5/1	20.0 (0.0-55.1)	-
Intermediate risk (1)	48/8	16.7 (6.1-27.2)	37/9	24.3 (10.5-38.1)	0.313
High risk (2-6)	255/63	24.7 (19.4-30.0)	266/91	34.2 (28.5-39.9)	0.085
CHA_2DS_2-VASc score					
Low risk (0)	0/0	0.0 (0.0-0.0)	0/0	0.0 (0.0-0.0)	-
Intermediate risk (1)	4/0	0.0 (0.0-0.0)	3/0	0.0 (0.0-0.0)	-
High risk (2-9)	309/71	23.0 (18.4-28.1)	305/101	33.1 (27.9-38.7)	0.008
HAS-BLED score[c]					
Low risk (0-2)	75/24	32.0 (21.4-42.6)	59/31	52.5 (39.8-65.3)	0.004
High risk (3-8)	238/47	19.7 (14.7-24.8)	249/70	28.1 (22.5-33.7)	0.073
Use of antiplatelet drugs					
Total (age ≥66 years)	313/155	49.5 (44.0-55.1)	308/141	45.8 (40.2-51.3)	0.423
$CHADS_2$ score					
Low risk (0)	10/0	0.0 (0.0-0.0)	5/1	20.0 (0.0-55.1)	-
Intermediate risk (1)	48/17	35.4 (21.9-48.9)	37/13	35.1 (19.8-50.5)	0.853
High risk (2-6)	255/138	54.1 (48.0-60.2)	266/127	47.7 (41.7-53.7)	0.374
CHA_2DS_2-VASc score					
Low risk (0)	0/0	0.0 (0.0-0.0)	0/0	0.0 (0.0-0.0)	-
Intermediate risk (1)	4/0	0.0 (0.0-0.0)	3/0	0.0 (0.0-0.0)	-
High risk (2-9)	309/155	50.2 (44.4-55.9)	305/141	46.2 (40.5-52.0)	0.400
HAS-BLED score[c]					
Low risk (0-2)	75/3	4.0 (0.0-8.4)	59/5	8.5 (1.4-15.6)	0.911
High risk (3-8)	238/152	63.9 (57.8-70.0)	249/136	54.6 (48.4-60.8)	0.066

[a]N/n = number of patients with atrial fibrillation/number of patients who used drugs. [b]Adjusted for age, sex, and education. [c]The HAS-BLED score does not include labile INR.

4.3 Association of atrial fibrillation with cognitive decline and dementia (Study III)

Of the 2685 dementia-free participants at baseline, 243 (9.1%) were classified as having AF. Over the 9-year follow-up period (mean per person 5.8 years, SD 2.2 years), 279 (11.4%) out of the 2442 AF-free older adults were detected to have incident AF. A total of 399 (14.9%) incident dementia cases were identified including 116 (6.2%) people with AD and 68 (2.5%) with vascular or mixed dementia.

Over the 9-year follow-up period, AF, as a time-varying variable, was significantly associated with a faster annual decline in MMSE score controlling for baseline demographic factors, lifestyle factors, cardiometabolic conditions, and cardiovascular diseases (β coefficient = -0.24, 95% CI: -0.31, -0.16) (**Figure 7**).

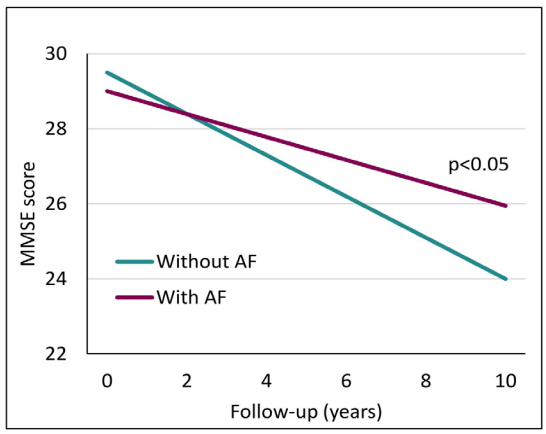


Figure 7. Average decline in the MMSE score by atrial fibrillation status from linear mixed-effects model. The model is adjusted for age, sex, education, excessive alcohol consumption, ever smoking, physical exercise, body mass index, hypertension, diabetes, dyslipidemia, coronary heart disease, and heart failure.

Multi-adjusted Cox regression models showed that, as a time-varying variable, AF was significantly associated with an elevated dementia risk (HR=1.40, 95% CI: 1.11-1.77). In the stratified analyses, the association between AF and dementia was statistically evident only among women and in *APOE* ε4 carriers (**Figure 8**). Excluding people with prevalent stroke/TIA (n=114) and censoring people at the dates when incident stroke/TIA occurred (n=72) did not substantially change the estimates.

With regard to dementia subtypes, AF was significantly associated with an greater risk of vascular and mixed dementia combined (HR=1.88, 95% CI: 1.09-3.23); this association was particularly evident among *APOE* ε4 allele carriers (HR=5.78, 95% CI: 1.26-26.50). The association of AF with risk of AD was not statistically significant (HR=1.33, 95% CI: 0.92-1.94) (**Table 7**).

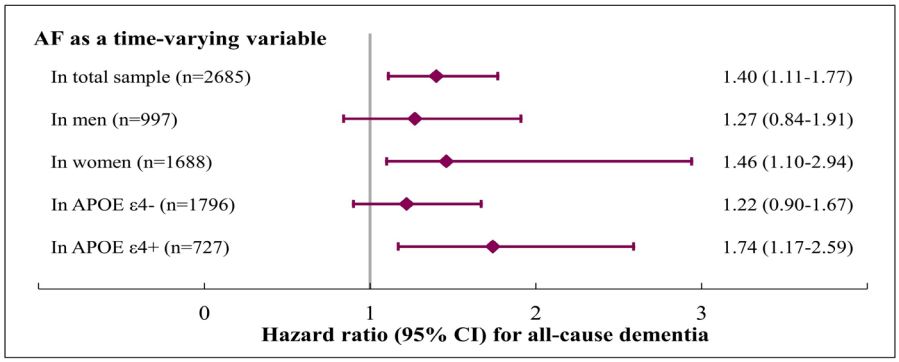


Figure 8. Hazard ratios and 95% confidence intervals (CI) of incident all-cause dementia associated with atrial fibrillation (AF) in the total sample and by sex and APOE genotype. Models are adjusted for age, sex, education, ever smoking, excessive alcohol consumption, physical exercise, body mass index, diabetes, hypertension, dyslipidemia, coronary heart disease, and heart failure.

Among participants with either prevalent or incident AF, propensity score-weighted Cox regression models showed a significant association between the use of anticoagulant drugs and a reduced risk of incident dementia over a 6-year follow-up period (HR=0.40, 95% CI: 0.18-0.92); the use of antiplatelet drugs was non-significantly associated with a higher dementia risk (HR=1.84, 95% CI: 0.99-0.42) (**Table 8**). Under the assumption of a causal association between anticoagulant therapy and a lower dementia risk, we estimated that around 54% of all dementia cases would have been hypothetically avoided if all participants with AF had received anticoagulant drugs (population attributable risk=0.46, 95% CI: 0.22-0.95).

Table 8. Hazard ratios (95% confidence intervals) of dementia associated with use of anticoagulant and antiplatelet drugs among participants with either prevalent or incident atrial fibrillation (n=470)

Antithrombotic drugs[a]	No. of participants	No. of dementia cases	Hazard ratio (95% confidence interval)[b]
Anticoagulant drugs			
Non-users	342	76	1.00 (Reference)
Users	128	14	0.40 (0.18-0.92)[c]
Antiplatelet drugs			
Non-users	187	25	1.00 (Reference)
Users	283	65	1.84 (0.99-3.42)[d]

[a]Treated as a time-varying variable. [b]Weighted by propensity score, and additionally adjusted for ever smoking, physical exercise, dyslipidemia, and body mass index. [c]p=0.031, [d]p=0.055.

Table 7. Hazard ratios (95% confidence intervals) of vascular or mixed dementia and Alzheimer's diseases associated with atrial fibrillation in the total sample and by sex and *APOE* genotypes

Atrial fibrillation (AF), as a time-varying variable[a]	Vascular or mixed dementia			Alzheimer's disease		
	No. of cases	Hazard ratio (95% confidence interval)		No. of cases	Hazard ratio (95% confidence interval)	
		Model 1[b]	Model 2[c]		Model 1[b]	Model 2[c]
Total sample (n=2685)						
AF, absent (n=2163)	43	1.00 (reference)	1.00 (reference)	123	1.00 (reference)	1.00 (reference)
AF, present (n=522)	25	2.11 (1.27-3.50)[e]	1.88 (1.09-3.23)[d]	43	1.38 (0.97-1.97)	1.33 (0.92-1.94)
Men (n=997)						
AF, absent (n=769)	11	1.00 (reference)	1.00 (reference)	31	1.00 (reference)	1.00 (reference)
AF, present (n=228)	13	2.61 (1.14-5.96)[d]	2.57 (1.10-5.99)[d]	13	0.97 (0.49-1.92)	0.81 (0.39-1.69)
Women (n=1688)						
AF, absent (n=1394)	32	1.00 (reference)	1.00 (reference)	92	1.00 (reference)	1.00 (reference)
AF, present (n=294)	12	1.66 (0.84-3.31)	1.33 (0.61-2.94)	30	1.59 (1.05-2.41)[d]	1.59 (1.02-2.49)[d]
APOE ε4 non-carriers (n=1796)						
AF, absent (n=1458)	28	1.00 (reference)	1.00 (reference)	68	1.00 (reference)	1.00 (reference)
AF, present (n=338)	16	2.12 (1.14-3.93)[d]	1.91 (0.97-3.75)	18	0.96 (0.57-1.62)	0.90 (0.51-1.59)
APOE ε4 carriers (n=727)						
AF, absent (n=601)	9	1.00 (reference)	1.00 (reference)	49	1.00 (reference)	1.00 (reference)
AF, present (n=126)	6	3.01 (1.03-8.84)[d]	5.78 (1.26-26.50)[d]	17	1.53 (0.87-2.68)	1.50 (0.83-2.72)

[a]Taking into account both prevalent atrial fibrillation (AF) at baseline and incident AF developed at follow-up. [b]Adjusted for age, sex, and education. [c]Adjusted for age, sex, education, ever smoking, excessive alcohol consumption, physical exercise, body mass index, diabetes, hypertension, dyslipidemia, coronary heart disease, and heart failure. [d]$p<0.05$. [e]$p<0.01$.

4.4 Association of atrial fibrillation with cerebral SVD markers (Study IV)

The mean age of the 540 participants in SNAC-K who underwent MRI examinations at baseline was 70.8 years (SD 9.1), 58.5% were women, and 40.4% obtained a university degree. A total of 39 (7.2%) participants were identified to have AF at baseline.

Logistic regression analysis showed that AF at baseline was significantly associated with an increased odds ratio (OR) of having cerebral infarcts on MRI (OR=3.98, 95% CI: 1.31-12.09) after adjusting for demographic factors, lifestyle factors, and chronic diseases. There was no significant association of AF with lacunes (OR=1.01, 95% CI: 0.33-3.08) and enlarged PVS (OR=5.71, 95% CI: 0.65-50.15) (**Table 9**).

Table 9. Cross-sectional associations of atrial fibrillation with cerebral infarcts, lacunes, and enlarged perivascular spaces at baseline (2001-2004)

MRI measures (as outcomes)	No. of subjects	No. of cases	Odds ratio (95% confidence interval)	
			Model 1[a]	Model 2[b]
Cerebral infarcts (yes vs. no)				
AF, absent	501	21	1.00 (reference)	1.00 (reference)
AF, present	39	8	4.49 (1.69-11.96)	3.98 (1.31-12.09)
Lacunes (yes vs. no)				
AF, absent	501	45	1.00 (reference)	1.00 (reference)
AF, present	39	5	1.20 (0.43, 3.30)	1.01 (0.33, 3.08)
Perivascular spaces (≥10 vs. <10)				
AF, absent	501	462	1.00 (reference)	1.00 (reference)
AF, present	39	36	2.68 (0.35, 20.69)	5.71 (0.65, 50.15)

[a]Model 1 was adjusted for age, sex, and education. [b]Model 2 was additionally adjusted for current smoking, alcohol consumption, physical exercise, body mass index, hypertension, diabetes, dyslipidemia, heart failure, and coronary heart disease.

In the analysis of longitudinal associations of baseline AF with alterations of cerebral SVD markers over the follow-up period, 248 participants who were free of cerebral infarcts on MRI at both baseline and follow-ups were included. Over the 6-year follow-up period, linear mixed-effects models showed that, as a time-varying variable, AF was significantly associated with a faster annual increase in WMH volume (β coefficient=0.45, 95% CI: 0.04, 0.85) and lateral ventricular volume (β coefficient=0.57, 95% CI: 0.13, 1.02) after controlling for demographic factors, lifestyle factors, and chronic diseases (**Figure 9**). AF was associated with an annual decline in total brain tissue volume, but the association was not statistically significant (β coefficient=-1.17, 95% CI: -3.68, 1.34).

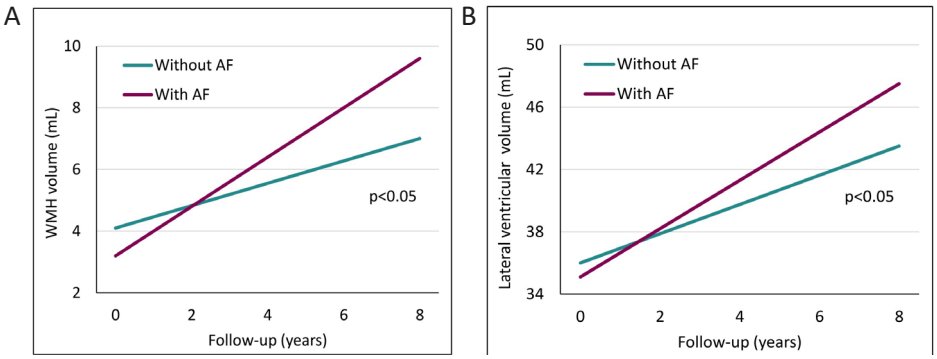


Figure 9. Average annual changes in (A) white matter hyperintensity (WMH) volume and (B) lateral ventricular volume from linear mixed-effects models, stratified by atrial fibrillation (AF) status. Models were adjusted for age, sex, education, current smoking, alcohol consumption, physical exercise, body mass index, hypertension, diabetes, dyslipidemia, heart failure, and coronary heart disease.

5 DISCUSSION

5.1 Summary of main findings

In this doctoral thesis, we investigated the temporal trend in the incidence of dementia from the late 1980s to the early 2010s in an urban Swedish population and further explored to what extent changes in a range of protective and risk factors for dementia could explain the temporal trend. Furthermore, we estimated the prevalence of AF in a general older population and examined the temporal trend in the use of antithrombotic drugs among older adults with AF. Moreover, we investigated the longitudinal association of AF with cognitive decline and risk of dementia, the cognitive benefits of anticoagulant drugs among people with AF, as well as the relationship between AF and various cerebral SVD markers detected on brain MRI. The main findings from this doctoral thesis are summarized as follows:

i) The incidence of dementia had declined from the late 1980s to the early 2010s in central Stockholm, Sweden, especially among women and in people with low education. Improvement in lifestyle, cardiovascular health, and cognitive reserve could only explain a small part of the decreasing trend in dementia risk (*Study I*).

ii) AF is common in people aged 60 years and older. The use of anticoagulant drugs among older people with AF increased from 2001-2004 to 2007-2010, especially in those with high risk of stroke or low risk of bleeding. However, still two-thirds of those with high risk of stroke remained untreated with anticoagulant drugs (*Study II*).

iii) AF is associated with an accelerated cognitive decline and a greater risk of all-cause dementia, especially vascular and mixed dementia, among older adults. The use of anticoagulant drugs, but not antiplatelets, is associated with a lower risk of incident dementia in older people with AF (*Study III*).

iv) Among older adults, AF is correlated with the presence of cerebral infarcts and associated with an accelerated increase in WMH volume and lateral ventricular volume in the absence of cerebral infarcts (*Study IV*).

5.2 The declining incidence of dementia

Study I showed direct evidence from two population-based cohorts that the incidence of dementia has declined in central Stockholm, Sweden. This is in line with an earlier Swedish study which inferred a decline in the incidence of dementia based on a relatively stable prevalence of dementia and a prolonged survival among dementia patients.[29] As described in the introduction section of this thesis, a declining incidence of dementia has been reported from population-based cohorts in Europe and North America such as the UK,[12,13] the Netherlands,[14] France,[15] and the USA.[16–18] In addition, a recent systematic review and meta-analysis integrating data from five population-based studies in Western high-income countries has suggested a favorable trend in dementia incidence.[157] When stratified by education level, a much greater decline in dementia incidence was seen among people with at most eight years of formal education (i.e., elementary school) than those with more education in our study. Only two US studies have examined dementia trends in different education groups, but showed a more evident decline among people with higher education.[17,18] However, it is difficult to directly compare the education levels between American and European populations since they were categorized and reported differently among studies. Beyond Western countries, investigations from Asian populations such as Japan[20] and China[158] have suggested an increasing incidence of dementia, although the increasing trends might be partly attributable to the great heterogeneity in study methodologies.[9]

Factors underlying the observed decreasing trends in dementia incidence in high-income countries are not entirely clear. Several hypotheses have been proposed, such as improved education, better management of major cardiovascular risk factors, and improvement in prevention of cardiovascular events over time,[159,160] which could lead to a compression of cognitive morbidity in old ages, manifested as delayed dementia onset and shorter disease duration in people with dementia.[161,162] Indeed, the education pattern has considerably changed over time in our study, with 78% of the SNAC-K population (2001-2004) having education above elementary level compared to only 49% in the KP cohort (1987-1989). In addition, work complexity and the proportion of people with active jobs were also substantially higher in the SNAC-K population. This rising level of formal education and improved psychosocial working conditions could have led to an increased stock of cerebral and cognitive reserve.[163] However, our study showed that accounting for the changes in various dementia protective and risk factors, including improved lifestyle, cardiovascular health, and cognitive reserve, over a period of two decades could only explain a small part of the observed decline in dementia incidence. This is consistent with previous findings from the Framingham Heart Study that the dropping dementia incidence could not be explained by improved education level and decreasing prevalence of vascular risk factors and cardiovascu-

lar diseases over the study period.[17] Nevertheless, our findings do not rule out a role for the examined dementia-related factors in explaining the decreasing trends, however, the role of other unexplored factors over the lifespan such as early life living conditions, leisure time activities during midlife, psychological stress, and exposure to toxic substance such as air pollution, warrants further investigations.

5.3 Prevalence of atrial fibrillation and use of antithrombotic drugs

Findings from Study II showed that the prevalence of AF among older adults from the general population appears to be slightly higher than previously reported. For example, the prevalence of AF in our study was 11% among people aged 72-78 years compared to a range of 3-10% in previous reports.[41,43,44] We reported a prevalence of 21% in people aged 90 years and above compared to a range of 10-17% in other studies.[40,43,45] As described in the introduction section of this thesis, discrepancies in the prevalence of AF among previous studies could be due to methodological variations. Given that our study used multiple sources including ECG, patient registers, and clinical examinations to identify AF cases from a general older population, it is likely that our study has captured more community-dwelling older adults with AF that had never come to medical attention than registry-based studies using only medical records to detect AF, thus reporting slightly higher estimates of AF prevalence.

Our findings that no AF patient with low risk of stroke (i.e., $CHADS_2$=0) at the time of baseline examination (2001-2004) was taking anticoagulant drugs were consistent with recommendations from consensus guidelines.[56] Women who have a CHA_2DS_2-VASc score of 1 (because of the sex) do not need anticoagulant treatment, since they are at true low risk of incident stroke.[57] Yet, whether anticoagulant therapy is needed among men with a CHA_2DS_2-VASc score of 1 is still a matter of debate;[164] this is possibly due to wide variabilities in the estimated risk of ischemic stroke among untreated men with a CHA_2DS_2-VASc score of 1.[54,165]

Our study also showed that less than one-third of AF patients with a high risk of stroke (i.e., $CHADS_2$ score ≥2 or CHA_2DS_2-VASc score ≥2) at baseline examination were using anticoagulant agents, which is considered low. On the other hand, compared to people using anticoagulant drugs, more than twice the participants with AF at baseline were using antiplatelets, which are not recommended to prevent ischemic stroke among older people with AF. As summarized in **Figure 1**, suboptimal anticoagulant treatment among older AF patients has been reported in many countries among previous register-based studies. Since our study included clinically undiagnosed (silent), thus untreated, older AF patients, the use of anticoagulant drugs in our study is even lower than register-based figures. Physicians are often reluctant to

prescribe anticoagulant drugs to very old people with AF due to concerns of major bleeding.[166] Indeed, our study showed that a high bleeding risk score is associated with not using anticoagulant agents among patients with a high risk of stroke. However, according to the ESC Clinical Practice Guidelines for AF, a high bleeding risk score shall warrant more frequent review of the patients rather than withdraw of anticoagulant treatment or inappropriate substitution with antiplatelets.[57]

Despite the suboptimal anticoagulant treatment among older people with AF at study baseline, the use of anticoagulant drugs among AF patients was substantially higher at the 6-year follow-up examination (2007-2010). This increase was particularly evident among people with high risk of stroke or low risk of bleeding. However, by the end of study follow-up, still around 70% of those at high risk of stroke were not on anticoagulant treatment. Secular trends in the use of anticoagulant agents among AF patients has been investigated by only a few register-based studies; most of these studies reported a suboptimal use of anticoagulant drugs by the end of study period despite a substantial increase during the follow-up period,[64,75,84,85] similar to our findings. While the observed improvement in the use of anticoagulant agents among AF patients may reflect dissemination of guideline recommendations into day-to-day clinical practice, more efforts are needed to further improve anticoagulant treatment among older people with AF.

5.4 Atrial fibrillation, cognitive decline, and dementia

In Study III, among a general older population aged 60 years and over, people with AF demonstrated a faster decline in global cognitive function and a greater risk of incident dementia compared to those without AF over a 9-year follow-up period. As shown in the literature (**Table 3**), the association of AF with cognitive outcomes appears to be more evident among middle-aged or younger-old adults; among very old people, findings are rather mixed. Inconsistencies in previous findings could be partially due to heterogeneous methodologies across studies, such as differences in sociodemographic characteristics of study populations, sample size, length of follow-up period, and proportions of dropouts. Importantly, given that the diagnosis of AF among older adults was often delayed,[49] our study accounted for incident AF in all the analyses in order to minimize the potential underestimation of the association between AF and cognitive outcomes. In our sub-analysis, the association between AF and a higher dementia risk remained even in the absence of clinical stroke/TIA, which is consistent with findings from several recent studies.[93,94,97]

Two main pathways have been proposed to underlie the link between AF and cognitive disorders, including cerebral hypoperfusion and vascular mechanisms such as cerebrovascular lesions.[121,167–169] Indeed, AF was associated with an increased risk of combined vascular and mixed dementia in our study, while

the association with the risk of AD was minimal. Several population-based studies have examined the link between AF and different dementia subtypes; some supported a higher risk of vascular dementia associated with AF,[103,170] while others suggested a higher risk for AD.[107,171] Yet most of these studies did not consider mixed dementia caused by both vascular and AD pathologies in the brain, which are of great clinical relevance given that most dementia cases are a mixture of cerebrovascular and neurodegenerative features that are difficult to disentangle, especially among very old people.[109] It has been suggested that in older people with insufficient load of AD pathologies to show clinical symptoms of dementia, additional vascular brain damage could hasten the development and progression of dementia syndromes.[109,142,172] In accordance with this view, our results showed an almost six-fold higher risk of combined vascular and mixed dementia associated with AF among *APOE* ε4 carriers, while no association was found among non-carriers of the ε4 allele. This indicates that the coexistence of AD pathologies related to *APOE* ε4 allele and cerebrovascular injuries associated with AF could result in a higher risk of dementia than either process alone.

Our results of an association of AF with accelerated cognitive decline and an increased risk of dementia have potential therapeutic implications. Few studies have examined cognitive outcomes associated with the use of anticoagulant drugs among older AF patients. A recent retrospective study covering all hospitalized patients with a diagnosis of AF in Sweden between 2006 and 2014 reported a 29% lower risk of dementia among patients with anticoagulant treatment than those without such treatment.[113] Similarly, a US study using healthcare data from Mayo Clinic reported a 20% lower risk of incident dementia over 10 years among AF patients using warfarin compared to those not on warfarin therapy.[173] A meta-analysis in 2019 pooling data from five longitudinal studies reported a 20% lower risk of incident dementia among AF patients using warfarin compared to those without anticoagulant treatment.[174] Our population-based study showed that the use of anticoagulant drugs (i.e., warfarin), but not antiplatelets, is associated with a 60% reduced risk of incident dementia among older patients with AF, indicating an additional cognitive benefit of anticoagulant treatment apart from stroke prevention. Our results are also in line with the current consensus guidelines that recommend anticoagulant drugs as the first-line treatment for stroke prevention, while the use of antiplatelets should be limited.[57] In the era of novel oral anticoagulant drugs (e.g., dabigatran, rivaroxaban, and apixaban), which offer comparable degrees of protection against ischemic stroke with a lower risk of intracranial hemorrhage than warfarin,[89,175] it is reasonable to hypothesize that novel anticoagulant drugs may have advantages over warfarin in terms of protection against accelerated cognitive decline and dementia in people with AF. Future studies are warranted to confirm this hypothesis.

5.5 Potential mechanisms underlying the association between atrial fibrillation and cognitive dysfunction

Several potential mechanisms have been proposed to explain the association between AF and cognitive dysfunction in old age, including pathophysiological cardiovascular changes associated with AF, pathways involved in the brain and heart connection, and structural brain abnormalities manifested as cerebral SVD, as summarized in **Figure 10**.

5.5.1 Cerebral small vessel disease

Structural brain abnormalities in old age manifested as cerebral SVD are usually of vascular origin or resulted from mixed pathologies,[176] which put older adults at an increased risk of cognitive decline and dementia.[119,177] Therefore, cerebral SVD may be an important neuropathological mechanism underlying the observed association of AF with cognitive decline and dementia. Yet current evidence has been so far limited regarding the longitudinal association of AF with various cerebral SVD neuroimaging makers. In Study IV, we investigated the associations of AF with a number of cerebral SVD markers including lacunes, PVS, WMH, and regional and global brain atrophy. We found that, in the absence of MRI-detected cerebral infarcts, AF is associated with an accelerated increase in WMH and lateral ventricular volume over the follow-up period. These results indicate that AF contributes to structural brain changes beyond brain infarction and that both cerebral microvascular and neurodegenerative pathways are possibly involved in this process, which mirrors the findings from Study III.

WMH reflect a process of axonal loss and demyelination as a consequence of chronic cerebral ischemia.[128,129] According to population-based studies, the presence and progression of WMH has been associated with several vascular risk factors including smoking, hypertension, and a history of cardiovascular diseases.[178–180] Current evidence from population-based studies that links AF to WMH is still scarce. In contrast to our results, longitudinal data from the Framingham Offspring Study and the ARIC study did not show a significant association between AF and changes in WMH volume.[131,133] It is worth noting that the age-specific prevalence of AF in both studies are low, which might have led to an underestimation of the association. With regard to brain atrophy, although the association between AF and total brain tissue loss was not statistically evident in our study, we did find an association of AF with increased lateral ventricular volume, which is consistent with previous findings from the ARIC study.[131] Enlargement of the lateral ventricle has been regarded as a surrogate marker of global brain atrophy due to the adaptive ability of the fluid-filled ventricular system.[181,182] Importantly, lateral ventricular enlargement not only reflects neurodegenerative neuron loss but also has been highly correlated with white matter lesions.[183–185]

5.5.2 Cerebral thromboembolism and hypoperfusion

Cerebral thromboembolism and hypoperfusion have been proposed as the main heart-brain pathways underlying the association of AF with structural brain abnormalities.[115,117] It has been well described that the abnormal hemostasis and hypercoagulable state in AF put patients at high risk of cerebral thromboembolisms and subsequent ischemic stroke.[186] However, clinically diagnosed strokes are only the tip of the iceberg of AF-related cerebral ischemia. Moreover, even in the absence of MRI-detected cerebral infarcts, AF can lead to substantial brain structural changes, as shown in Study IV. In addition to macroscopic brain infarction, cardiac and cerebral thromboembolic phenomenon may result in the accumulation of cerebral microinfarcts, which are beyond the resolution of conventional MRI, leading to subsequent WMH and brain atrophy.[187,188]

AF could also lead to cerebral hypoperfusion by virtue of beat-to-beat variations and reductions in cardiac output and blood pressure.[167] Evidence supporting a direct association between AF and cerebral hypoperfusion has recently emerged, as the Icelandic AGES-Reykjavik Study showed that people with persistent AF had lower cerebral blood flow and brain blood perfusion compared to the paroxysmal AF group and control group.[189] A meta-analysis of 24 cross-sectional studies reported that a high WMH load was strongly associated with lower cerebral blood flow, however, whether cerebral hypoperfusion precludes WMH or vice versa remains unclear.[190] Furthermore, it has been proposed that cerebral hypoperfusion induces brain capillary degeneration and suboptimal energy delivery to neurons, which could further result in a progressive loss of brain tissue.[191]

Overall, it is likely that AF contributes to brain lesions through various mechanisms affecting both the macro- and micro-environment in the brain. Larger longitudinal population-based neuroimaging studies are needed to assess the relationship of AF with different pathophysiological and neuropathological pathways.

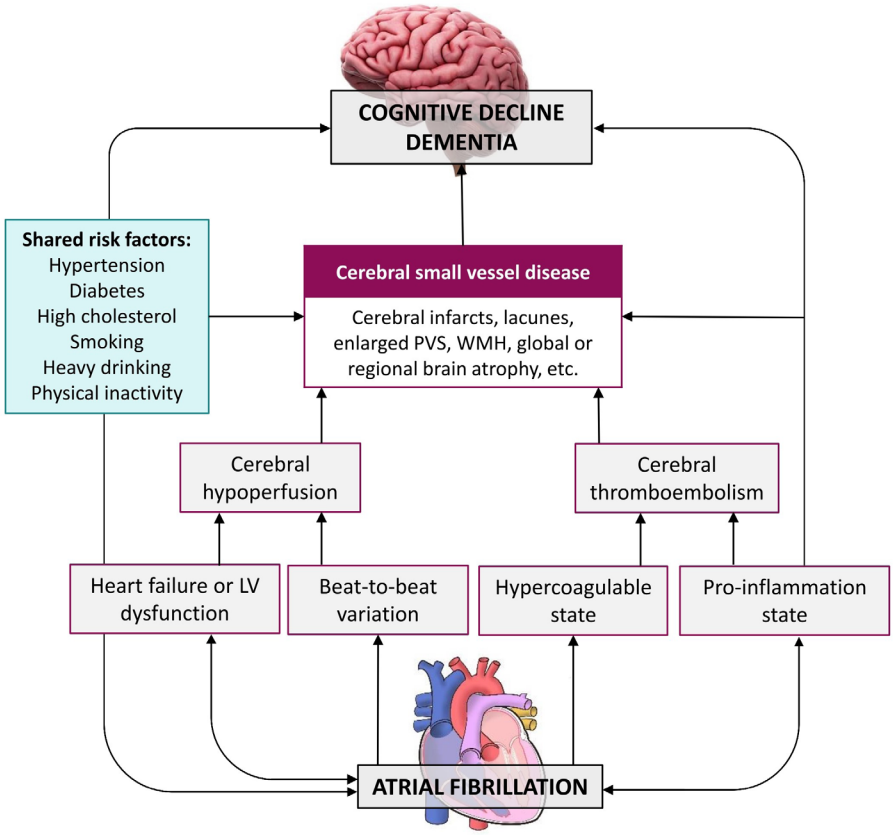


Figure 10. A schematic overview of potential mechanisms linking atrial fibrillation to cognitive decline and dementia. LV =left ventricle.

5.6 Methodological considerations

In this doctoral thesis, two population-base studies, the KP (only in Study I) and the SNAC-K study, with similar study designs and protocols were used. Both studies have a generous sample size and comprehensive data were collected by almost the same data collection group of trained health-care professionals as objectively as possible following standard procedures. However, methodological issues may arise in all epidemiological studies, among which systematic error and random error are of most consideration.

5.6.1 Systematic error (biases)

Systematic errors in epidemiological studies are broadly divided into three categories: selection bias, information bias, and confounding.

Selection bias

Selection bias comes about when the relationship between the exposure and the outcome differs for the participants and the non-participants in the study, resulting in either underestimation or overestimation of the association. Selection bias can occur both during the sampling and recruitment processes at study baseline and during the study follow-up where attrition might happen. In both KP and SNAC-K, the participation rates at baseline are considered high for older populations (76.4% vs. 73.3%). People who declined to participate at baseline could be older, less educated, had more chronic diseases, and thus more likely to experience the study outcomes (e.g., dementia in Study III) than those who participated. On the other hand, those who declined could also be younger, still working (e.g., <65 years), and thus less likely to experience dementia. Due to the fact that people who declined to attend the baseline examination had shorter survival time than those who participated, it is likely that the first scenario has occurred in this project, leading to an underestimation of the associations. During the follow-up examinations, given that the data collection group spent great efforts to keep the participants in the study, the dropout rates was low in both KP and SNAC-K cohorts and most of the non-participation occurred because of death (refers to Figures 2 and 3 in the introduction section). In Study I and Study III, no participant was lost to follow-up due to death because we were able to include in the analytical samples people who died during the study period by using information from death certificates. However, we could still have underestimated the association between AF and dementia if participants died before developing dementia. Taken together, considering the non-participation at baseline and during the follow-up, it is likely that an underestimation of the observed associations might have occurred in this project.

Information bias

Information bias can occur when the information collected from the participants is erroneous. Such information is regarded as misclassified, either differential or nondifferential, if the variable is categorical and the error leads to a person being classified into a wrong category. Nondifferential misclassification occurs when the exposure or disease (or both) is misclassified but the misclassification is not dependent on the person's other status. This type of misclassification often leads to a dilution of the true association. In contrast, differential misclassification happens when the exposure is misclassified differently according to the person's

disease status, which often results in under- or overestimation of the associations. In general, to avoid misclassification, the trained heath care professions in both KP and SNAC-K assessed the participants as objectively as possible following standard procedures at both baseline and follow-up examinations.

The potential misclassification of AF and cognitive outcomes (i.e., global cognition and dementia) in this doctoral project is more likely to be nondifferential, given that the identification of AF is unlikely to be dependent on the person's cognitive status and vice versa. Although multiple sources are used in Studies II-IV to detect AF cases among the participants, we might still have missed some asymptomatic cases (silent AF). In addition, MMSE as a measure of global cognitive function may not be sensitive enough to detect subtle changes in certain cognitive domains, especially among highly educated people such as the SNAC-K participants. Therefore, the association of AF with cognitive decline, dementia, and cerebral SVD markers in this thesis might have been underestimated. With regards to use of medications, because the collection of medication information of each participant partially relied on the medication containers participants brought to the interview, differential misclassification of use of medications might arise if cognitively impaired persons forgot to bring certain drugs. However, since proxies of cognitively impaired participants were always consulted and the examining physician carefully reviewed the medical charts of each participant, the misclassification of use of medications is minimized. The lack of data on the duration of antithrombotic treatment and the quality of anticoagulant control represents another limitation. However, this might have limited influence on results in Study III because the anticoagulant control is generally good in Sweden.[192]

Confounding

A confounder is a factor that is associated with both the exposure and the outcome, but not in the causal pathway. In all the four individual studies in this thesis, we dealt with the issue of confounding bias by either stratifying or adjusting the analyses for potential confounders. However, unmeasured or unknown confounders could still be present, and thus we cannot completely rule out the possibility of residual confounding.

In pharmacoepidemiological studies, confounding by indication of drug use often occurs. This type of confounding arises when people who take a drug differ from those who do not based on the medical indication for which the drug is prescribed. In Study III, physicians might be reluctant to prescribe anticoagulant drugs to AF patients who had cognitive impairment, therefore, the protective effect of anticoagulant drugs against dementia could be overestimated. We dealt with this confounding by indication by using the propensity score to balance as many characteristics as possible that could differ between drug users and non-users, however, residual confounding might still exist.

5.6.2 Random error

Random error includes sampling error and measurement error. In epidemiological studies, sampling error is incurred when the characteristics of a population are estimated from a subsample of this population. Since not everyone from the population is included in the sample, statistics of the sample generally differ from the entire population. Sampling error can be reduced by increasing the sample size. Measurement error can occur due to limited precision in the tools, devices, or methods when measuring study variables. Measurement error can be reduced by repeating the measurements on the same individual and average them.

5.6.3 Generalizability

The ultimate goal of epidemiological studies is to generalize study findings to other populations or countries. However, the above-mentioned sampling errors and systematic biases might limit the generalizability of study results, which could be particularly relevant for prevalence or incidence studies. Given that the KP and SNAC-K cohorts included a sample of healthier Caucasians with higher socioeconomic status from the Kungsholmen area of central Stockholm, the generalizability of Study I and Study II might be limited in less wealthy populations with different demographic and disease characteristics. For instance, the decreasing incidence of dementia in Study I might not be generalizable to Asian populations in which the cardiovascular profile might be different from the European populations. Indeed, an increasing trend in dementia incidence has been reported from China and Japan. On the other hand, investigations on the association between an exposure and a disease which has solid biological plausibility are less dependent on the statistical representativeness of the sample. It is believed that it is the biological knowledge, insight, and conjecture, instead of representativeness of the study subjects, that makes for a proper generalization.[193,194] Therefore, generalizability is made possible through not only a representative sample but also a good understanding of the biological principles and skillfully controlling for potential confounders.

6 CONCLUSION

1. From the late 1980s to the early 2010s, the incidence of dementia had declined among older adults in central Stockholm, Sweden; this decline is particularly evident among women and in people with low education. Improvements in lifestyle, cardiovascular health, and cognitive reserve over the study period could explain only a small part of the decline.

2. AF is more common than previously reported among people aged 60 years and over. The use of anticoagulant drugs among older people with AF increased from 2001-2004 to 2007-2010, especially among those at high risk of stroke or low risk of bleeding. However, still two-thirds of older people with AF who were at high stroke risk remained untreated with anticoagulant drugs.

3. AF is associated with an accelerated global cognitive decline and an increased risk of all-cause dementia, and vascular and mixed dementia in particular, among older people. Use of anticoagulant drugs, but not antiplatelet drugs, may prevent older adults with AF from developing dementia.

4. AF is associated with an accelerated increase in white matter lesions and faster brain atrophy in the absence of cerebral infarcts.

7 RELEVANCE AND IMPLICATIONS

Global population aging has led to a dramatic increase in the proportion of older adults who are susceptible to age-related diseases such as dementia. Dementia has been recognized as a global public health priority, and the vast burden this devastating disorder imposes on both individuals and the society has led to continued global efforts to tackle the dementia epidemic. Therefore, studying the temporal trends in the incidence of dementia in the general older population, identifying modifiable risk factors for dementia such as AF, and exploring the potential neuropathological mechanisms linking AF to cognitive aging are critical for future planning and allocation of society's resources as well as for preventive interventions. For instance, while the absolute number of people with dementia will continue to increase alongside population aging, the finding of a declining incidence of dementia since the 1980s indicates that the future burden of dementia might be milder than previously anticipated.

Findings from this doctoral thesis also have several clinical implications. First, our study revealed that AF is more common among older adults from the general population than previously reported, which calls for the initiation of screening program to improve the detection of asymptomatic AF both in the clinic settings and in the general population. Second, the underuse of anticoagulant drugs in AF patients at both baseline and six years later indicates that the dissemination of evidence-based medicine (guidelines) into the clinical settings still needs to be improved. Third, the independent association of AF with cognitive decline and dementia may help to identify AF patients at risk of dementia and allow for timely initiation of appropriate medical and preventive strategies (e.g., patient-centered intervention) to reduce dementia risk. These findings may also support the inclusion of cognitive assessments in AF patients in the clinical diagnostic work-up as well as in future clinical trials involving AF patients. Fourth, our findings on the cognitive benefit of warfarin among older patients with AF underlines the importance of proper treatment of AF to not only prevent ischemic stroke but also delay cognitive decline and dementia onset. Future randomized controlled clinical trials on novel anticoagulant drugs among AF patients shall consider cognitive outcomes as a primary endpoint. Finally, our MRI findings that AF contributes to both cerebrovascular lesions and neurodegenerative features in the brain may aid in future research examining the specific neuropathological mechanisms behind the AF-dementia association. Furthermore, these findings may help to develop optimal anticoagulant regime and improve the risk estimation of ischemic stroke and dementia among older people with AF.

8 FUTURE DIRECTIONS

This doctoral thesis contributes new knowledge to the existing literature regarding the occurrence of dementia and AF, the association of AF with cognitive and brain aging, and the cognitive benefits of anticoagulant treatment among older adults. Yet future research is needed to verify our main findings and to address the new research questions this thesis brings forward.

First, future investigations are warranted to further examine factors other than those included in our study in explaining the decline in dementia incidence, in order to facilitate the development of intervention strategies and inform better policy decisions. Although we took into account the most relevant protective and risk factors of dementia, the role of other factors, such as early childhood conditions,[195] reproductive spans and number of pregnancies among women,[196] leisure time physical activities in midlife,[197] cancer,[198] and toxic exposures (e.g., air pollution),[199,200] remains to be investigated.

Second, given that novel oral anticoagulant drugs are readily available in the market, it remains to be seen whether anticoagulant treatment has improved among older AF patients since the launch of such drugs. In addition, since novel anticoagulant drugs have several advantages over warfarin, whether they have stronger long-term protective effect than warfarin against dementia remains unclear, although initial data on this regard have provided some favorable evidence.[201] Moreover, given the plausibility of hypoperfusion hypothesis behind the AF-dementia association, whether rhythm control drugs or AF catheter ablation can also benefit cognitive function needs to be investigated.

Finally, the exact biological and neuropathological mechanisms underlying the association between AF and cognitive dysfunction need to be better understood, in order to inform optimal therapeutic and preventive interventions of cognitive disorders in older AF patients. In particular, larger population-based neuroimaging studies with better scanning resolutions are needed to elucidate the association of AF with cerebral microinfarcts, microbleeds, and hypoperfusion. Additionally, whether and to what extent markers of cerebral SVD mediate the association of AF with cognitive decline and dementia is to be investigated in larger imaging studies with a longer follow-up period.

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11 APPENDIX

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991-2019

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.

Rehnman Jenny. The role of gender in face recognition. (Stockholm University)

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.

Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.

Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

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Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.

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Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

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Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.

Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

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Seblova Dominika. Causal effects of education on cognition – How do we generate evidence?

Berggren Rasmus. Cognitive development and educational attainment across the life span.

Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.

Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.

Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.

Avelar Pereira Bárbara. Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

Lucas Morin. Too much, too late? Drug prescribing for older people near the end of life.

Lieke de Boer. Dopamine, decision-making, and aging: Neural and behavioral correlates.

Stina Ek. Predictors and consequences of injurious falls among older adults: A holistic approach

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